psychoactives

MDPI

Review

The Noscapine Saga: Unravelling a Valuable Jewel from a Poppy Pod—Past, Present and Future

Anjali Priyadarshani [1,*], Rishit Bhatia [1] and Muniba Shan [2]

[1] Department of Zoology, Kirori Mal College, University of Delhi, Delhi 110007, India
[2] Department of Life Sciences, Kirori Mal College, University of Delhi, Delhi 110007, India
* Correspondence: anjali18kumar@kmc.du.ac.in; Tel.: +91-9911406185

Abstract: Noscapine is a naturally occurring alkaloid isolated from *Papaver somniferum*, commonly known as opium poppy or bread seed poppy. It edges over other opioids as it lacks addictive, sedative or euphoric effects. This review chronicles the saga of endeavours with noscapine, from modest efforts in the mid-1950s to its present anticancer potential and futuristic hope in combating COVID-19. We comprehensively searched for publications including noscapine- and noscapinoid-relevant keywords in different electronic databases such as PubMed, Google Scholars, Elsevier, Springer Link and Science Direct up to June 2023. We excluded those in a language other than English. Noscapine has long been used as an antitussive and suppresses coughing by reducing the activity of the cough centre in the brain. A great number of water-soluble noscapine analogues have been found to be impressive microtubule-interfering agents with a superior antiproliferative activity, inhibiting the proliferation of cancer cell lines with more potency than noscapine and bromo-noscapine. With enhanced drug delivery systems, noscapine has exerted significant therapeutic efficacy in animal models of Parkinson's disease, polycystic ovary syndrome, multiple sclerosis and other disorders. Furthermore, the merit of noscapine in crossing the blood–brain barrier makes it a putative candidate agent against neurodegenerative and psychiatric diseases. Its long safety record, widespread availability and ease of administration make it an ideal candidate for fighting several life-threatening conditions. Recent promising docking studies onnoscapine with main protease (Mpro) of SARS-CoV-2 paves the way for combinatorial drug therapy with anti-viral drugs and is hopeful in fighting and triumphing over any future COVID-19 pandemic.

Keywords: opioid; antiangiogenic; anticancer; antitussive; apoptosis; noscapine; noscapine analogues; polycystic ovary syndrome

Citation: Priyadarshani, A.; Bhatia, R.; Shan, M. The Noscapine Saga: Unravelling a Valuable Jewel from a Poppy Pod—Past, Present and Future. *Psychoactives* **2024**, *3*, 1–21. https://doi.org/10.3390/psychoactives3010001

Academic Editor: Ricardo Dinis-Oliveira

Received: 30 November 2023
Revised: 4 January 2024
Accepted: 5 January 2024
Published: 10 January 2024

1. Introduction

With the unearthing of a precious jewel from a humble poppy pod, opium has fascinated civilisations throughout history, and has a history reaching back to 3400 BC [1]. It was widely used in Mesopotamian society, among others, due to its euphoric and therapeutic effects. Poppy extracts were useful to the Greeks, Romans and Arabs for a variety of things, with the results ranging from sedative to euphoric effects [2]. About 25 alkaloids are naturally present in opium: morphine and codeine were the first isolated (Figure 1). A crystalline compound containing noscapine was successfully separated from opium in 1803, thanks to a Parisian pharmacist by the name of Jean-François Derosne. It was probably used with morphine meconate at the time, however. Noscapine was first isolated from Derosne's salt in 1817 by Professor Pierre-Jean Robiquet of the Paris École de Pharmacie, who is largely credited with its discovery [3].

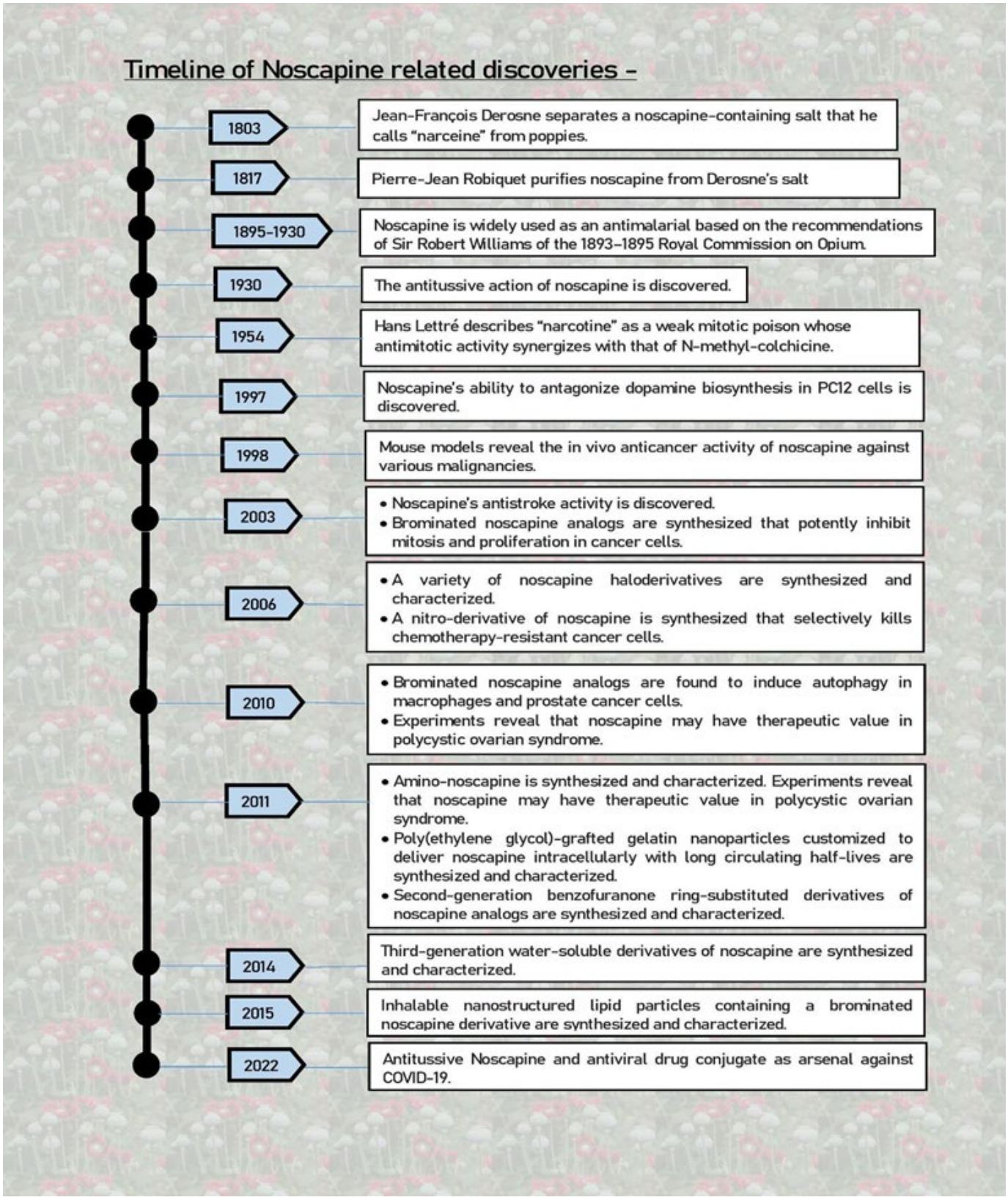


Figure 1. Evolution of noscapine from the humble beginnings of being a cough suppressant to a promising arsenal against COVID-19.

As early as 4000 BC, refined derivatives of the poppy plant spread throughout many communities, eventually infecting China and India, and making their way to Europe by the 16th century [1]. Paracelsus, the physician of the Renaissance, enabled the extraction of morphine from poppies, which joined opium as a common ingredient in pharmacies [4]. Thanks to the persistent efforts of researchers over the years who sought to extract physiologically active components from poppies, opium-derived medicines are still being used in clinical settings today. Noscapine is one such derivative that stands out for having qualities exceptionally conducive to good health [5]. Opium was used in India as a prophylactic and curative antimalarial drug in the late 19th century. This practice persisted until a thorough investigation refuted its purported antimalarial effects in 1930, consigning noscapine to a time of relative obscurity. However, it turned out that the general opinion that noscapine had no medical value was incorrect. In actuality, over the course of the following few decades, the wide-ranging clinical uses of noscapine were gradually discovered [6,7]. It has been nothing short of astounding to follow this path from the early discovery of its antitussive qualities to its potential in treating illnesses including strokes, different malignancies and polycystic ovary syndrome [PCOS], to name a few (Figure 1) [7–9].

2. Methodology

We comprehensively searched for publications including noscapine-relevant keywords in different areas in five different electronic databases, PubMed, Google Scholar, Elsevier, SpringerLink and ScienceDirect, up to June 2023, focusing on the new ones. The retrieval of articles was carried out by analysing their abstracts, and afterwards, further articles that were retrieved from their references were also reviewed so as to make the search complete according to the inclusion criteria. We excluded non-English articles, conference papers and studies that overlapped.

3. Unveiling Noscapine's Physico-Chemical Portrait

The phthalide is quinoline alkaloid noscapine can be found in opium poppies, *Papaver somniferum*, in amounts ranging from 4% to 12% of their latex. The names Capval, Coscopin, Terbenol, Tusscapine, Narcompren and Narcosine are only a few of the many names for this substance. Noscapine is a fine white powder with a strong bitter flavour and no smell. Its chemical formula is $C_{22}H_{23}NO_7$ and its molecular weight is 413.42052 g/mol. Only ether, alcohol, NH_4OH and heated KOH and NaOH solutions exhibit limited solubility of this alkaloid. It is practically insoluble in vegetable oils. It does, however, show solubility in acetone and benzene. The salt version of noscapine, noscapine HCl, is notable for having a high water solubility, which is essential to its therapeutic uses [10–13].

4. Nature's Alchemy behind the Making of Noscapine into a Conqueror

The noscapine production route starts with [S]-reticuline and includes intermediates including [S]-scoulerine, [S]-canadine and [S]-N-methylcanadine. To acquire a thorough comprehension of noscapine production in the opium poppy, Dang et al. carried out a detailed analysis of four successive enzymes that convert 1-hydroxy-N-methylcanadine into narcotoline hemiacetal [14,15].

After the cytochrome P450 CYP82Y1 was identified, its role in catalysing the first and crucial step in the production of noscapine—the 1-hydroxylation of [S]-N-methylcanadine into 1-hydroxy-N-methylcanadine—was thoroughly examined. The cytochrome P450 CYP719A21, another vital enzyme, makes it easier for [S]-tetrahydrocolumbamine to change into [S]-canadine [14].

Two additional cytochrome P450 enzymes conduct hydroxylation at the C13 and C8 positions in the core structure of protoberberine. The hydroxylation at C8 results in ring opening and the creation of an aldehyde group. In the noscapine biosynthetic pathway in *Papaver somniferum*, hydroxylation at C8 occurs after acetylation at C13, thereby introducing a protective group, which is later removed by a carboxylesterase. This deletion triggers a rerganisation that results in the creation of a cyclic hemiacetal [14–16].

Noscapine synthase, the final enzyme in noscapine biosynthesis, is a member of the short-chain dehydrogenase/reductase family of enzymes. This enzyme, which is mostly found in the laticifers of the opium poppy, catalyses the conversion of narcotine hemiacetal into noscapine [15,17].

5. Understanding the Pharmacology of Noscapine: Unravelling the Design of the Conqueror

Noscapine, administered orally, shows fast and effective absorption. Studies reveal its bi-exponential kinetics, with intravenous administration resulting in a 13 min distribution half-life. Its oral bioavailability is approximately 30%, with some variation [18,19].

Metabolism studies indicate the presence of various metabolites, with no liver damage observed in mice. Noscapine activates p34cdc2 kinase, crucial for inducing apoptosis. It also triggers the JNK pathway, particularly effective in paclitaxel-resistant cancers [20,21].

In angiogenesis, noscapine inhibits HIF-1α, reducing VEGF expression. It influences the NF-κB pathway, suppressing proteins that aid cancer cell survival. Additionally, noscapine displays antifibrotic effects, inhibiting TGF-β-induced differentiation [22].

The pharmacokinetic data from both animals and humans further enhance our understanding of noscapine's absorption and clearance rates. Intravenous administration leads to an average plasma concentration of 7.88 μg/mL within 5 min, declining to undetectable levels at 4 h. In humans, the oral administration of 50 mg results in rapid absorption, yielding a plasma concentration of 182 ng/mL after one hour. The half-life is approximately 124 min, with an absolute oral bioavailability of around 30%. Four hours post-administration, its concentration in the blood is undetectable, indicating an average total body clearance of 4.78 L/h with a distribution volume of 5.05 L [18,19].

6. Noscapine Analogues: Deciphering the Brigade of Noscapine

Owing to its low toxicity and established cytotoxic activity, many noscapine analogues have been developed. Table 1 summarises the biological evaluation of noscapine and noscapine analogues exhibiting multifaceted actions. They affect autophagic processes in addition to centrosome clustering and spindle poles, which cause cell death. For example, it was found that Red-Br-Nos induced autophagy in human PC-3 prostate cancer cells in less than 12 h. This analogue also resulted in the production of reactive oxygen species (ROS), which are necessary for the induction of autophagy [23–25].

Table 1. Summary of biological evaluation of noscapine and water-soluble analogues of noscapine.

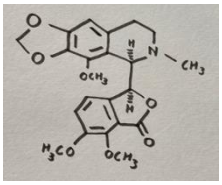
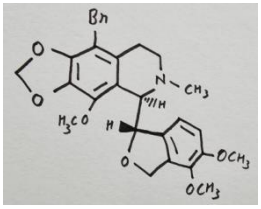
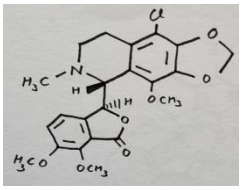
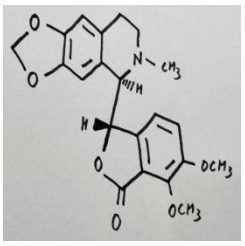
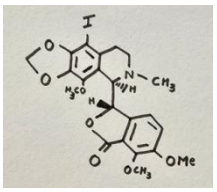
Name	Noscapine—Effects and Mechanisms	Chemical Structure	References
Noscapine—a benzylisoquinoline alkaloid	• Authorised antitussive drug • Potential drug for cancer via apoptotic effects, antiangiogenesis • Anti-stroke • Exhibits an anti-inflammatory effect • Potential drug for PCOS via regulating theca cell hyperproliferation		[13]
Name	**Analogues of Noscapine—Effects and Mechanisms**	**Chemical Structure**	**References**
Red-Br-Nos	**Targets human prostate cancer** (a) Promotes apoptosis without the aid of caspases but with the help of ROS and is much more potent than noscapine. (b) Causes DNA damage in a way that is dependent on ROS, resulting in PC-3 cells exhibiting spindle multipolarity and high-grade centrosome amplification. (c) Cell death occurs due to abnormal mitotic spindles with high-grade multipolarity.		[25,26]

Table 1. *Cont.*

9-chloronoscapine and its derivative EM015	**Targets ovarian and T-cell lymphoma cancers** (a) Most effective derivative against glioma U87 cells when compared to other halonoscapine analogues. (b) EM015 binds to tubulin and is a more active analogue of noscapine. (c) Triggers the apoptotic process in U-87 human glioblastoma cells to an extent greater than noscapine.		[27–32]
9-bromonoscapine	**Targets breast, prostate, lung cancers** (a) Triggers programmed cell death after a G2/M arrest in PR- and ER-negative breast cancer cells; blocks prostate cancer cell lines at the G2/M boundary with a higher binding affinity to tubulin than noscapine. (b) Causes alterations in the transmembrane potential of the mitochondria, which, in PC-3 cells, triggers the intrinsic apoptotic cascade. (c) Modifies the expression of Bcl2 proteins, which are responsible for inducing caspase-dependent apoptosis and controlling the release of downstream molecules. (d) Causes centrosome amplification, which, in turn, causes spindle multipolarity and cancer cell death when combined with centrosome de-clustering.		[12,30,31,33–35]
9-iodonoscapine	(a) Triggers the apoptotic process in U-87 human glioblastoma cells to an extent greater than noscapine.		[30,32]

The protective function of ROS-mediated autophagy after Red-Br-Nos therapy in PC-3 cells was initially documented by Karna et al. Additionally, they found that Red-Br-Nos promotes apoptosis without the aid of caspases but with the help of ROS. Furthermore, it was discovered that Red-Br-Nos caused DNA damage in a way that was dependent on ROS, which caused PC-3 cells to exhibit spindle multipolarity and high-grade centrosome amplification.

This paper documented the first instance of Red-Br-Nos causing centrosome amplification via de novo centrosome creation, which took place during a brief S/G2 halt. Cell death resulted from the formation of abnormal mitotic spindles with high-grade multipolarity. Red-Br-Nos's unique mechanism sets it apart from other ROS inducers, DNA-damaging drugs and anti-microtubule drugs [25,26].

To facilitate solubility and colonic distribution, Madan et al. employed bioresponsive guar gum microspheres [GGMs] to encapsulate Red-Br-Nos with β-CD and methyl-β-cyclodextrin [methyl-β-CD]. Red-Bromo-Nos solubility rose around 10.7- and 21.2-fold in a phosphate buffer saline when mixed with β-CD and methyl-β-CD, respectively. This increased solubility correlated with an approximately two- and three-fold decline in the IC50 for Red-Br-Nos-β-CD-GGMs and Red-Br-Nos-methyl-β-CD-GGMs, respectively, compared to the analogues free of GGMs [27].

Noscapinoids, in addition to their induction of autophagy due to the release of reactive oxygen species (ROS), also exhibits anti-inflammatory properties, a property in common with the microtubule-binding drug colchicine. By assessing various molecular models of competition binding between colchicine and Br-Nos, it has been indicated that the tubulin binding site of Br-Nos lies close to or overlaps with the tubulin binding site of colchicine [25,28].

To understand the anti-inflammatory activity of noscapine and its brominated analogues, Zughaieret al. conducted studies in which it was found that its brominated analogues cause the inhibition of the release of the cytokine TNFα and chemokine IP-10/CXCL10 from the macrophages. In this way, they are able to reduce inflammation without risking macrophage viability. This study also resulted in ensuring that even if the cells were challenged with autophagy, causing TLR- or non-TLR-binding ligands, the anti-inflammatory properties of the brominated analogue of noscapine persist unaffected [29].

Numerous compounds of halonoscapine have been investigated. For example, when 9-chloronoscapine was compared to other halonoscapine analogues, like 9-bromonoscapine and 9-iodonoscapine, it was found to be the most potent derivative against glioma U87 cells due to its simplicity of production. 5-Br-Nos is another halonoscapinoid that has been found to disrupt mitotic division and restrict HeLa cell proliferation. EM015, which is a derivative of 9-chloronoscapine, exhibits higher activity than noscapine, in addition to its tubulin-binding activity. These analogues, such as 9-Br-Nos, 9-iodonoscapine and 9-chloronoscapine, trigger the apoptotic process in U-87 human glioblastoma cells to an extent greater than noscapine [30–32].

The derivative 9-Br-Nos, known for increasing the G2/M population in MCF-7 breast cancer cells, also shows promise against hormone-insensitive human breast cancers cells, causing apoptosis once they have entered G2-M arrest [30,31].

Furthermore, 9-Br-Nos demonstrated efficacy against human tumours when xenografts of MDA-MB-231 cells, which lack progesterone and oestrogen receptors, were inserted into nude mice. The mice in the treatment group were given 9-Br-Nos orally via gavage, whereas the mice in the control group were given water. The tumour volume was significantly reduced and the survival rate increased four-fold in the experimental group. The potency of this noscapinoid in suppressing MCF-7 cell proliferation has been shown to be 40 times that of the parent molecule [31].

It was found to be useful against tumour cells that were resistant to drugs without producing cytotoxic effects in healthy tissues. The same analogue was demonstrated to be effective against human prostate cancer cells. No toxicity was ascertained by Aneja et al. in normal rapidly proliferating tissues like that of the bone marrow and gut. 9-Br-Nos acted on a prostate cancer cell and arrested it at the G2/M border with a greater tubulin-binding affinity than noscapine. It also induces changes in the potential of the mitochondrial transmembrane, eventually causing the activation of the intrinsic apoptotic cascade in PC-3 cells. In the process, possible alteration of the expression of Bcl-2 proteins occurs. These proteins can activate caspase-dependent apoptosis and modulate the release of downstream factors. Further, after the oral intake of 9-Br-Nos, it was observed that tumour growth was inhibited in intratibial prostate cancer xenografts. A different study exposes the harmonious relationship between docetaxel and 9-Br-Nos for the treatment of prostate cancer. The results varied drastically when noscapine was administered along with lower doses of docetaxel, and it produced greater proapoptotic activity in comparison to the administration of docetaxel alone. This signifies that the above combination improves the overall wellbeing of docetaxel-treated patients and can reduce toxicity [33,34].

9-Br-Nos were encapsulated with β-CD and methyl-β-CD by Madan et al., supporting an 11-fold [β-CD] and 21-fold [methyl-β-CD] rise in the solubility of the phosphate buffer solution. Once the IC50 value was lowered, the modified bromonoscapinoids uncovered a vigorous the rapeutic index. A nanostructured lipid particle species of 9-bromo noscapine [9-Br-Nos-RR-NLP] which is inhalable and rapidly released was devised. This resulted in an alteration in the polymerisation of tubulin in non-small cell lung cancer cells compared to the parent compound. According to Jyoti et al., enhanced cytotoxicity, cellular uptake and apoptosis were observed in A549 non-small cell lung cancer cells, once administered with the inhalable 9-Br-Nos-RR-NLPs. The IC50 value was found to be lower than the 9-Br-Nos suspension, 9-Br-Nos-NLP and its non-rapid-release form [12,35].

7. Noscapine's Maiden Medicinal Role: A Remedy for Coughs

Noscapine, discovered in 1930, is a potent antitussive. Unlike codeine, it lacks addictive properties due to its minimal analgesic and sedative effects. It does not primarily bind to the μ-opioid receptor [18]. As depicted in Figure 2, its effectiveness shines in suppressing coughs induced by ACE inhibitors. Noscapine antagonises bradykinin-mediated constriction, a mechanism linked to ACE-inhibitor-induced coughing. ACE inhibitors lead to bradykinin accumulation, causing bronchoconstriction, mucous production and histamine release, resulting in inflammation and coughing. Noscapine reduces the histamine-induced contractility of certain arteries [18,19].

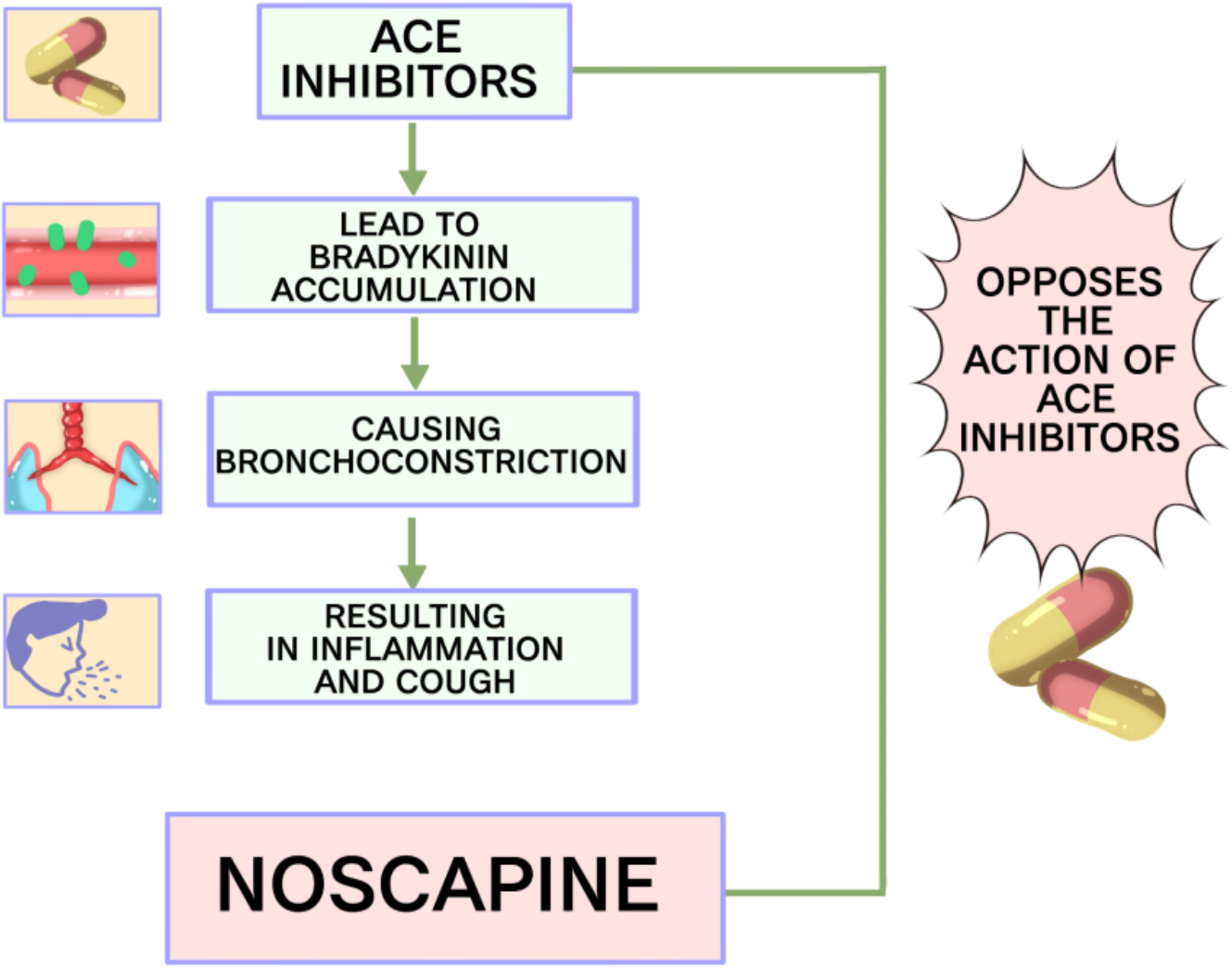


Figure 2. Noscapine's inaugural medicinal role as a remedy for cough.

Studies have shown noscapine's impressive results, with 90% of hypertensive patients experiencing complete relief from ACE-inhibitor-induced coughing within 10 days [19]. Opioid receptors are not responsible for noscapine's antitussive effects. Patients with hypertension sometimes require lower doses of antihypertensive drugs alongside noscapine. In summary, noscapine's antitussive potency is linked to its modulation of the bradykinin responses, making it a promising therapy for coughs induced by ACE inhibitors [7,18,20].

8. Noscapine's Novel Role in Stroke Treatment: Giving an Old Cure a New Life

Stroke is one of the main causes of death in many developed nations. Tissue plasminogen activator [rt-PA] in its recombinant form, the main medication for ischemic strokes that the FDA has approved, must be administered within a three-hour window of when the stroke first occurs. Its application is strongly constrained by a list of strict contraindications, which include ailments like bleeding diathesis, recent major surgery or trauma within the previous three months [7,21].

Innovative stroke treatments are becoming more and more necessary as a result of these restrictions. According to the research, bradykinin, which is secreted in the brain following localised ischemia in mice, is crucial. Bradykinin-B2-receptor-deficient animals showed lower morbidity, smaller infarct volumes, less cerebral edema and higher overall survival rates [13,22].

Noscapine, renowned for its noncompetitive bradykinin-receptor-antagonistic activity, has shown promise in preventing organ ischemia–reperfusion injury. Further research into this substance's suitability as a stroke treatment was inspired by this trait. Using a rat model of brain edema, researchers found that noscapine dramatically reduced the cerebral damage in neonatal rats that had experienced hypoxic ischemia [23].

Interesting results from a small clinical research work were revealed. Noscapine was given orally to patients within a 12 h window exhibiting ischemic stroke symptoms, and this significantly decreased their fatality rates from 80% to 20%. Importantly, there were no documented cases of hemorrhaging, and the noscapine-treated survivors showed a significantly better recovery than the control group. These findings hold great promise for the potential role of noscapine as a valuable tool in mitigating the devastating effects of stroke [13,23].

9. Noscapine's Expanding Armory against Cancer

Noscapine, a substance first noted for its antitussive and anti-stroke qualities, has drawn significant interest for its potential as a cancer treatment [13]. Its exceptional efficacy as an antineoplastic agent against a wide variety of malignancies has been revealed by the research. Phase I/II clinical trials are now being conducted, which represents a substantial advancement towards its potential medical use [24]. Noscapine and its analogues, derived by modifying specific sites of the parent compound, show promise in combating cancer. They function as potent centrosome de-clustering agents, disrupting the microtubule dynamics. Cancer cells with amplified centrosomes cluster them to survive mitosis, but these drugs prevent this clustering, leading to spindle multipolarity, cell cycle arrest and, ultimately, cell death. Noscapine and its analogues induce alterations in the microtubule dynamics, affecting their interaction with kinetochores during mitosis, activating the checkpoint of the spindle assembly and leading to mitotic arrest and eventual cell death (Figure 3). Additionally, they alter the tubulin heterodimer configuration, acting as tubulin-stabilising agents. Bromonoscapine and reduced bromonoscapine induce centrosome amplification and, along with this, result in centrosome de-clustering, spindle multipolarity and cancer cell death, making these compounds potential cancer-selective chemotherapeutics due to their specificity to cancer-related anomalies like supernumerary centrosomes. Furthermore, noscapine alters the dynamics of microtubule assembly by stoichiometrically binding to them without significantly promoting or inhibiting microtubule polymerisation. It extends the duration of microtubules in an attenuated or paused state. By binding to tubulin, noscapine changes its conformation, arresting the cell at mitosis without causing major deformities in the cellular microtubules. This alteration eliminates kinetochore tension, leading to chromosome congression failure and the loss of tension across sister kinetochores, subsequently activating the spindle checkpoint.

Numerous cancer cells, including drug-resistant varieties, exhibit cell growth inhibition when treated with noscapine, but healthy cells are left unaffected. This exceptional selectivity opens the door to a promising new approach to targeted cancer therapy. Furthermore, noscapine is a different possibility in the battle against cancer due to its effect on microtubules, which differs greatly from that of other drugs [11,13,21].

It is interesting to note in Figure 3 that noscapine causes metaphase arrest and death in dividing cells, highlighting its potential as an anticancer drug. By altering the kinetics of microtubule assembly, it affects cell division and achieves its goal [25]. Noscapine can lessen the tension between kinetochores, but it does not change the tubulin polymer/monomer ratio, according to the research. As a result, the spindle checkpoint is triggered, stopping the continuation of the mitotic cycle [26].

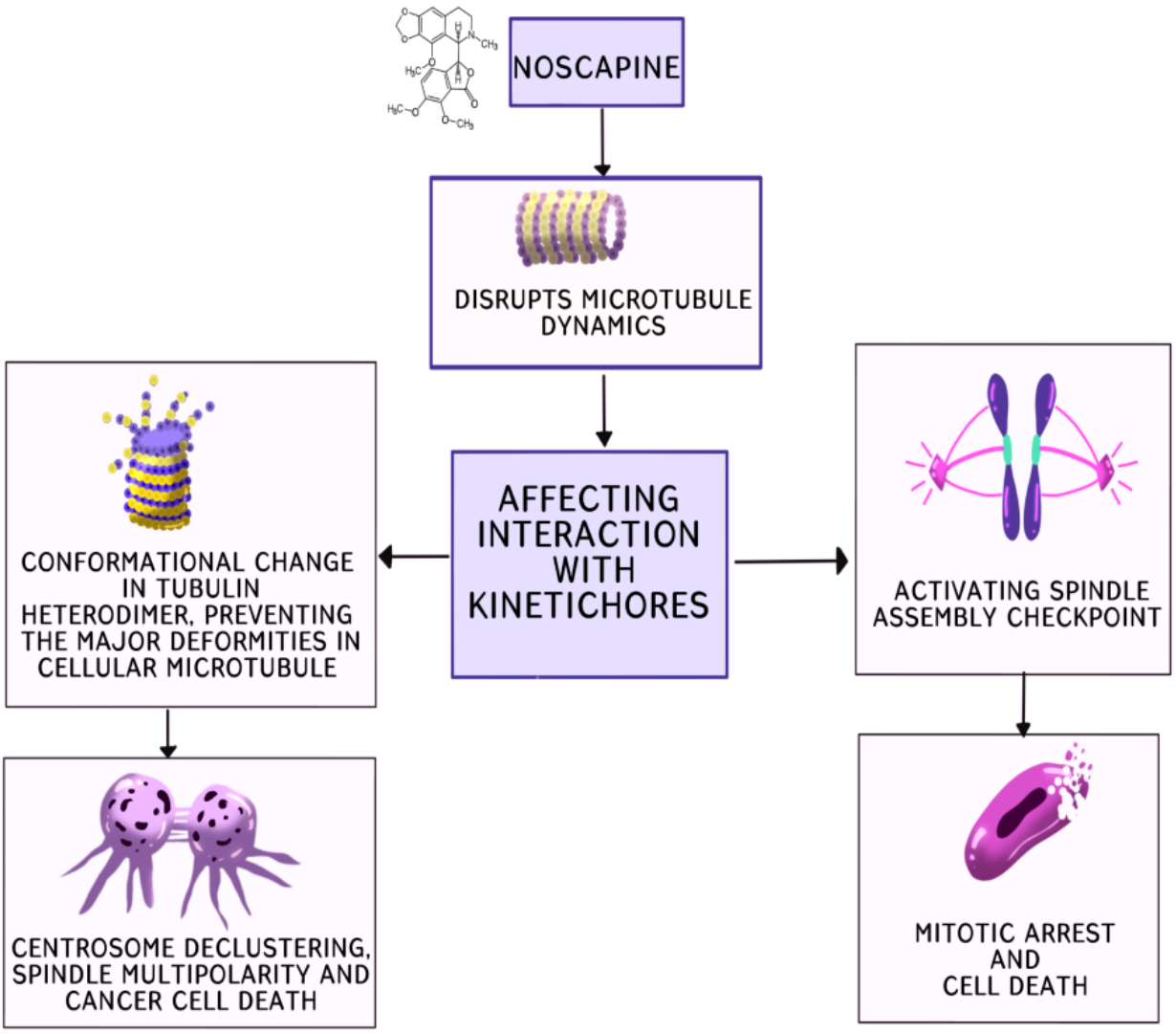


Figure 3. Noscapinoids: potential cluster bombs including centrosome de-clustering.

Furthermore, tubulin undergoes a conformational shift upon the stoichiometric binding of noscapine, which alters the assembly of the microtubules without hampering the total microtubule mass. The activation of the spindle assembly checkpoint as a result of this modification to the assembly dynamics causes mitotic arrest and eventually apoptosis, highlighting its anticancer potential [24,26]. Noscapine is a viable possibility for cancer therapy due to its notable low toxicity and lack of immune system suppression.

Noscapine may revolutionise cancer treatment since more studies are being undertaken to see how effective it is against different forms of cancer [27].

9.1. Non-Small Cell Lung Cancer

Noscapine, notably in the form of noscapine HCL [Nos], has emerged as a promising anticancer drug in the field of treating non-small cell lung cancer [NSCLC]. Its promise in both in vitro and in vivo conditions has been highlighted by extensive research [24]. H460 cells were exposed to different concentrations of Nos in a thorough investigation, proving how powerfully it can limit cell proliferation. Nos impressively induced apoptosis, a vital component in the fight against cancer. Using Nos to treat xenografted H460 tumours in female athymic Nu/nu mice resulted in significantly smaller tumor sizes, further demonstrating its effectiveness [28,29].

The study's most significant finding was that the modulation of important proteins, such as PARP, Bax and caspase-3, was crucial in the Nos-induced inhibition of tumour growth. Notably, Nos and gemcitabine showed an increased apoptotic impact, suggesting a potential synergistic strategy against NSCLC [30]. It is significant that the work goes into the molecular elements, illuminating Nos's role in triggering apoptosis via the mitochondrial pathways. This discovery holds great promise for the creation of NSCLC medicines that work [31].

Noscapine has drawn interest due to the subpar clinical outcomes of the available therapies for NSCLC. Its promise as a strong chemotherapeutic drug has been proven by vast research conducted both in vitro and in vivo. Notably, noscapine exhibits synergistic effects when combined with other medications like gemcitabine and cisplatin, possibly altering the treatment options for people with non-small cell lung cancer [30–32].

9.2. Glioblastoma

Due to the tough blood–brain barrier, glioblastoma, a particularly difficult form of cancer, presents considerable treatment challenges. Glioblastoma patients commonly have a dismal outlook because the existing chemotherapeutics frequently fail to overcome this barrier. Noscapine, however, shows promise as a treatment option because it can cross the blood–brain barrier and stop the proliferation of glioblastoma cells. Although frequent dosing is required due to its short plasma half-life, Madan et al. have investigated novel formulations to prolong its absorption into the body [28].

Notably, noscapine does not cause much toxicity in vital regions like the dorsal root ganglia or different organs, suggesting that it has the potential to be used as a non-neurotoxic medication. Furthermore, it does not result in peripheral neuropathy, a problem with some microtubule-targeting drugs. To assess its impact on intracranial pressure, however, further investigation is required [29,30].

Noscapine shines as a possible ally in the field of glioblastoma treatment. It has the ability to suppress the development of TMZ-resistant glioma cells and work in concert with present chemotherapeutics to boost their efficacy. Noscapine is advantageous for people receiving radiation therapy because it also increases radiation sensitivity. Noscapine has potential as a non-neurotoxic treatment option for glioblastoma, but more research is necessary [31–34].

9.3. Thymic Carcinoma

Though extremely uncommon and categorised as orphan illnesses, thymic tumours have a noteworthy relationship with myasthenia gravis, affecting roughly 10–15% of those who have the condition. Thymoma is a cancer that presents serious challenges for patients [7,35].

Noscapine appears to be a promising therapy option, which is encouraging. In mice with E.G7-OVA thymoma cells, a study showed that noscapine administration, either intraperitoneally or intragastrically, resulted in a decrease in tumour size [25,35]. In addition to this encouraging outcome, DNA fragmentation was seen within 8 h of noscapine treatment, and there was a 50% rise in apoptotic bodies within 24 h [24,35,36].

Additional research using methods like the TUNEL assay verified that DNA fragmentation and apoptotic nuclei occurred in both HeLa cells and E.G7-OVA cells. These results highlight the possibility of using noscapine as a thymoma therapy [25,35]. As research develops, it provides the groundwork for possible treatment trials, giving people struggling with this uncommon but difficult ailment hope [27].

9.4. Ovarian Cancer

Standard chemotherapeutics like paclitaxel and cisplatin [CIS] can cause human ovarian cancer cells to develop resistance, which is frequently accompanied by unsettling toxicities and poor solubility. This highlights the need for novel ovarian cancer treatment strategies [37,38]. A possible option is noscapine, a non-toxic benzylisoquinoline derivative. Noscapine was found in a study to attach to and suppress the proliferation of ovarian cancer cells while leaving normal cells unaffected. This offers a potential remedy for the problems with drug resistance that are frequently encountered when treating ovarian cancer [39–44].

In addition, noscapine inhibits mitosis in paclitaxel-resistant ovarian cancer cells via interacting differently with tubulin from paclitaxel. This novel mode of action has the potential to overcome beta-tubulin mutation-related resistance [13,45–47]. Additionally, noscapine and cisplatin work together synergistically. This not only prevents drug-resistant cells from proliferating but also alters the expression of genes associated with apoptosis, increasing the number of tumour cells that undergo this process [48–52]. It is interesting to note that noscapine reverses tumoural resistance, improving the efficacy of doxorubicin and vincristine, two other chemotherapeutics. This multifaceted strategy underlines the potential of noscapine as a useful addition to the toolkit for treating ovarian cancer [53–56].

To sum up, noscapine appears to be a potential contender in the fight against ovarian cancer, providing fresh hope for patients dealing with drug resistance and the difficulties posed by conventional chemotherapies. Noscapine has the potential to transform the therapeutic approaches to and enhance the outcomes for patients suffering with this severe disease because of its unique modes of action [7,24,56–59].

9.5. Gastric Cancer

Gastric cancer is one of the most prevalent types of cancer globally, especially in the Eastern parts of Asia, Europe and the Andean regions of South America. The alarming 9 million instances reported annually globally highlight the need for more expedient treatment options, particularly those utilising innovative methods. Noscapine has emerged as a promising candidate for the treatment of stomach cancer due to its extensive anticancer characteristics [7,24,27].

Noscapine's effect on stomach cancer cells was carefully explored in a study performed by Liu et al. It was conclusively proven by extensively studying four different cell lines that noscapine caused apoptosis, greatly reducing cell viability. Notably, treatment with noscapine resulted in a striking decrease in the number of BGC823 cells that were still alive [60,61]. The researchers expanded their investigation by performing studies on mice that had tumour xenografts. Noscapine was given intravenously to each group of these animals at regular intervals. Positively, compared to the control group, this treatment plan led to the development of smaller tumours. Caspases-3 and 9 were also activated, which supported the involvement of these pathways even more [28,62].

Noscapine elevated important proteins like Bax and cytochrome c while downregulating Bcl2, according to further study. The Bax/Bcl-2 ratio, a critical sign of apoptosis via the mitochondrial pathways, was significantly raised by this change. Caspases-3 and 9 were again activated, which further suggested the involvement of these pathways [62]. These encouraging preclinical results strongly imply that noscapine therapy has significant potential for patients with gastric cancer, providing some hope in the search for more efficient treatments for this difficult cancer [63].

9.6. Colon Cancer

The treatment of colorectal cancer is incredibly difficult because it is notorious for being resistant to modern chemotherapy. According to a study, the efficiency of noscapine is hugely dependent on its capability to cause G2/M arrest and apoptosis, and also on the p53/p21 factor and on the susceptibility of cancer cells in the colon [HCT116] to the drug.

The maximum sensitivity to noscapine was seen in cells with intact p53, whereas the highest resistance was seen in cells without p53. The crucial function of p53 was demonstrated by the reinstatement of noscapine-induced apoptosis after p53 was introduced into previously deficient cells [64–67].

It is interesting to note that p21-null cells continued to resist apoptosis in the presence of high p53 levels, demonstrating that p53 is required but insufficient for noscapine-mediated apoptosis and that p21 has a proapoptotic role. These findings suggest that noscapine holds potential as a therapeutic agent for treating colon cancer, particularly in cases where the p53 and p21 expression levels can be modulated [65–69].

In addition, another study discovered that noscapine activated the PI3K/mTOR signalling pathway while reducing the PTEN expression in specific colon cancer cells. Furthermore, it was observed that noscapine significantly induced apoptosis in these cells, indicating its potential as an anticancer agent for colon cancer treatment. This is in line with the general consensus that focusing on vital metabolic enzymes can improve drug-induced apoptosis in cancer cells and possibly result in more efficacious treatments. Combining targeted medications with metabolic inhibitors is a viable way to tackle cancer treatment resistance, according to these pooled insights. This may mark a significant development in the fight against cancer, especially for notoriously difficult cases like colorectal cancer [62,64,69].

9.7. Breast Cancer

Noscapine has proven to be an impressively effective treatment for breast cancer both in vitro and in vivo. It showed promise in slowing the growth of human and murine breast tumours when administered to animals, mostly by inducing apoptosis. In vivo studies showing a remarkable 80% regression in human breast cancers further supported this promise in hormone-receptor-positive MCF-7 breast cancer cells [60]. The ability of noscapine to kill triple-negative hormone-resistant breast cancer cells is particularly encouraging. It showed a discernible decrease in the tumours caused by MDA-MB-231 xenografts in mice. Even more intriguing is the fact that it showed a synergistic impact when paired with doxorubicin, indicating a potentially advantageous combination for triple-negative breast cancer patients, who currently have limited treatment options [70,71].

Innovative noscapine-loaded estrone-conjugated gelatin nanoparticles [Nos-ES-GNs] were developed to address the issue of noscapine's short biological half-life, poor absorption and limited solubility. These nanoparticles had an IC50 value that was almost 50% lower than the free medication, demonstrating improved efficacy. Additionally, the study showed that estrone-conjugated noscapine-loaded gelatin nanoparticles accumulated more in MCF-7 cells with oestrogen receptor positivity than in MDA-MB-231 cells with oestrogen receptor negativity, indicating the possibility of precision targeting [71].

Additional research, such as that carried outby Chouguleet al., highlighted the dose-dependent antitumour impact of noscapine. Triple-negative breast cancer was treated with oral noscapine [550 mg/kg] and doxorubicin [1.5 mg/kg], which showed a three-fold improvement in antitumour activity. Additionally, research using approximately 36 M of noscapine showed that it inhibits the multiplication of breast cancer cells [70]. NPN [VinPhe-Nos], a noscapine derivative, has become a promising contender for the treatment of invasive malignancies. It significantly reduced the growth of new malignant colonies and effectively stopped the cell cycle during crucial stages. Studies also demonstrated NPN's capacity to attach to tubulins and alter their tertiary structure, presenting an interesting line of inquiry [72–74].

Noscapine had a negligible effect on microtubules, whereas NPN emerged as a more powerful disruptor, severely harming microtubules and preventing their reconstruction. These results highlight the potential of noscapine and its derivatives to completely alter the way that breast cancer is treated [61].

9.8. Prostate Cancer

Many people have serious concerns about prostate cancer, especially in light of the fact that, despite improvements in detection and understanding, its metastatic forms are still challenging to treat. Although its early detection has improved, there are currently few viable therapeutic choices for metastatic prostate cancer. Docetaxel is currently used at its highest tolerated dose, but this can have serious adverse effects, including peripheral neuropathy, gastrointestinal toxicity, immunosuppression and myelosuppression. A primary priority is the hunt for a chemotherapeutic drug that is both more efficient and less crippling [34,75].

Noscapine exhibited potential in lowering the tumour volume in prostate cancer in a promising research work conducted by Barken et al. Noscapine-treated mice had considerably fewer primary and metastatic tumours than the animals in the control group over the course of two months. Additionally, the group that received noscapine treatment had a greatly decreased rate of metastasis. Comparatively to the control group, where metastasis occurred in 90% of instances, noscapine administered orally each day at a dose of 300 mg/kg led to a marked decrease in metastasis. Given this, it is possible that noscapine can stop or slow the progression of prostate cancer to the lymph nodes [34].

Remarkably, there was no statistically significant difference in lung metastasis between the treatment and control groups. This implies that further research is needed to ascertain whether noscapine can genuinely improve metastasis-free survival in humans.

There is hope for more effective treatments with less disabling side effects thanks to this encouraging breakthrough in the investigation of noscapine's influence on prostate cancer [75].

10. Exploring Noscapine's Diverse Application beyond Conventional Roles

Figure 4 schematically shows the potential use of noscapine in alleviating many pathological conditions and the mechanisms behind it. It may help with disorders like pheochromocytoma by inhibiting dopamine production. Research using rat adrenal pheochromocytoma cells (PC12) revealed a marked decrease in dopamine levels without any side effects.

Additionally, noscapine shows promise for treating PCOS due to its antiangiogenic properties. When radiolabelled with Technetium-99m, it accumulated most in the liver, spleen, kidney and ovaries, with a doubled uptake in PCOS rats. However, noscapine's antiviral potential is limited, highlighting the need for stronger antivirals against viruses like HPV [76–78].

Furthermore, chronic inflammation, seen in conditions like metabolic syndrome and cancer, is regulated by inflammatory and anti-inflammatory agents. Noscapine exhibits anti-inflammatory effects, reducing proinflammatory factors. Studies demonstrate its effectiveness against carrageenan-induced inflammation and bradykinin-induced inflammation. Brominated noscapine shows even more potent anti-inflammatory effects, inhibiting cytokines and chemokines without toxicity. It also proves effective in models of septic inflammation [29].

In the context of PCOS, noscapine administration in PCOS-induced rats at a dose of 120 mg/kg body wt. led to a reversal of anovulation and restoration of cyclicity. It also restored healthy follicular development and hormone levels. In RU486-administered PCOS rats, elevated levels of testosterone and estradiol were observed, along with decreased FSH and increased LH. Noscapine treatment reversed these hormone imbalances, offering potential therapeutic benefits for PCOS [9]. In another study, direct radiolabelling of noscapine and its biodistribution in various organs and specific uptake in PCOS show its utility for imaging ovarian pathology. The increased ovarian uptake in PCOS opens the avenue for 99mTc-noscapine in PCOS diagnostics and therapeutics [9].

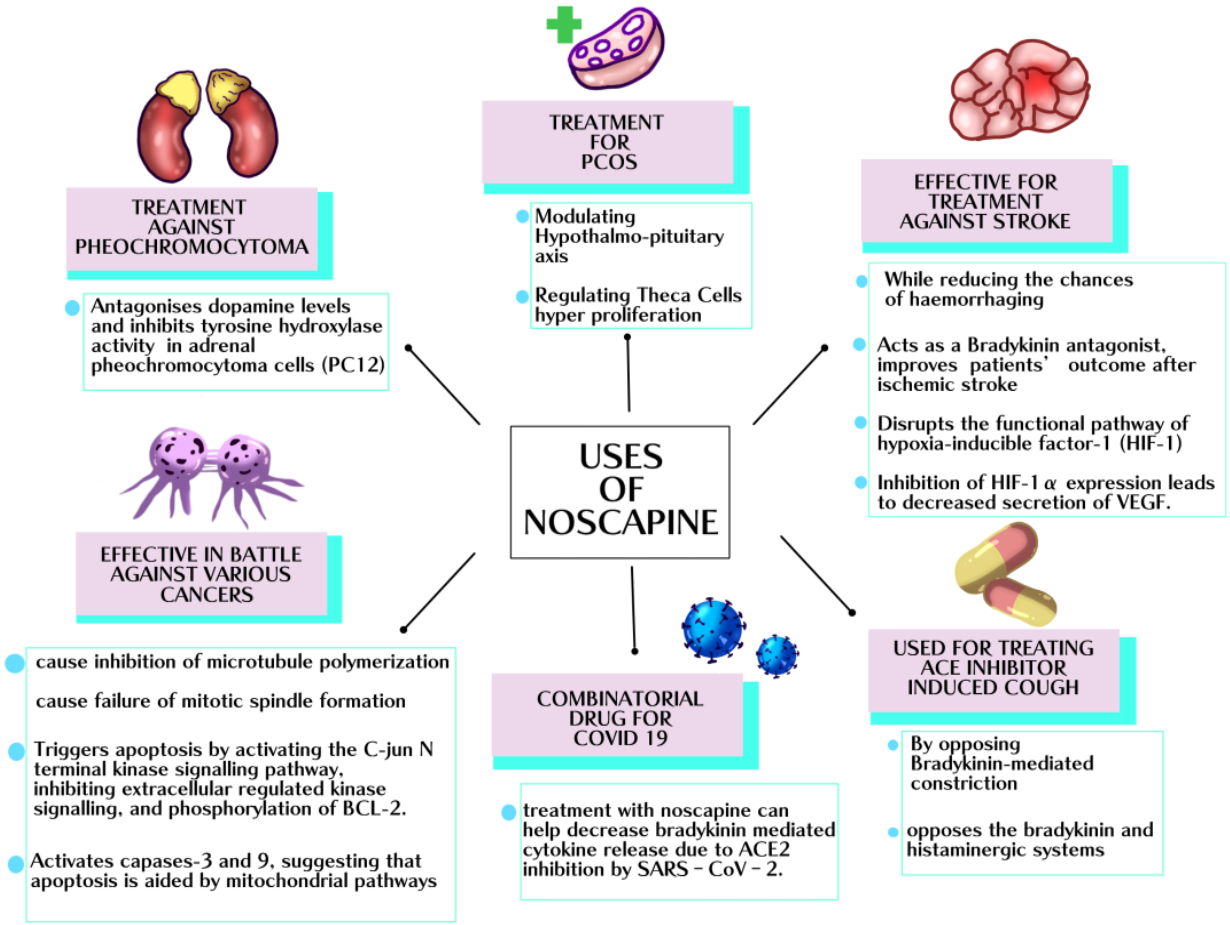


Figure 4. The possible signalling pathways modulated by noscapine in alleviating cancer and other pathological conditions.

11. SARS-CoV-2 and Noscapine

After first appearing in Wuhan, China, in December 2019, COVID-19 has since spread throughout the world, killing a large number of people. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus that causes COVID-19 and has caused pandemic conditions worldwide [79]. A significant number of COVID-19 outpatients experience the bothersome symptoms of coughing and dyspnea, which can last for a long

time and negatively impact patients' quality of life. The research has demonstrated that noscapine in combination with licorice was beneficial in early COVID-19 trials [80]. A study by Kumar et al. suggested for the first time that the way noscapine works to combat viruses is by preventing the creation of viral proteins [81].

Globally, the coronavirus epidemic has claimed a great deal of lives. Therefore, the development of potent counteragents against the novel coronavirus illness (COVID-19) is urgently needed. Although several antiviral medications have been used therapeutically, there has been little evidence of recovery, which has increased the need for a new and improved understanding in order to develop successful therapies. In clinical trials, noscapine, an authorised antitussive medication with favourable effects on the lung linings, was strategically used in conjunction with antiviral medications. Noscapine was used in combination with antiviral medications (galidesivir, favipiravir, umifenovir, hydroxychloroquine and chloroquine). This study found that the noscapine–hydroxychloroquine (Nos–Hcq) combination has a substantial binding affinity for SARS-CoV-2's major protease (Mpro), which plays a crucial biological role in the infection and spread of the virus. Further prioritisation of in vitro and in vivo research for medicines with robust binding against Mpro of SARS-CoV-2 are made possible by the proposed combinatorial therapy of noscapine [82].

12. Discussing the Future Potential for the Noscapine Family: A Plethora of Alternatives

Noscapine, originally a cough suppressant, has proven to be versatile beyond its initial purpose. It offers a wide range of benefits, particularly for patients dealing with malignancies. Teams have extensively tested its toxicity in vitro, in animal models and in patients, confirming its minimal toxicity at the usual doses [82–84]. While high doses may lead to side effects like nausea and abdominal discomfort, these occurrences are rare [85]. Noscapine and its derivatives show promise as anticancer agents due to their subtle modulation of the microtubule dynamics, distinguishing them from other more aggressive microtubule-targeting drugs. Novel water-soluble noscapinoids have been synthesised, demonstrating superior microtubule-interfering properties and enhanced antiproliferative activity compared to the parent compounds [6,11].

Noscapine has emerged as a compelling alternative to traditional cancer therapies. Unlike treatments like radiation, chemotherapy and surgery, which can weaken the body without significantly reducing mortality risk, noscapine offers advantages like oral bioavailability and a safe pharmacological profile. Despite requiring a high effective dosage for apoptosis induction in mutated cells, it remains cost-effective as a natural opium alkaloid. This affordability increases its accessibility to a wider population. Importantly, noscapine selectively induces apoptosis in cancer cells by targeting the microtubules, binding stoichiometrically to tubulin and arresting the cell cycle at the metaphase. It exhibits cytotoxicity exclusively towards mutagenic cells, sparing healthy tissues and organs [69].

Noscapine not only stands on its own as a potent anticancer agent but also enhances the effectiveness of other treatments like radiation therapy and chemotherapy, particularly against drug-resistant strains of cancer [39].

Ongoing phase I/II trials in multiple myeloma patients underscore its potential for wider applications. As research advances, noscapine may evolve into a transformative "wonder drug". Yet, challenges persist, including the need for an efficient total synthesis of biologically active noscapine. Synthetic routes have been explored, but yield and purity remain issues. Bischler–Napieralski cyclisation is a common reaction, and biosynthesis using enzymes presents another commercial avenue. Additionally, synthetic analogues, such as 9′-bromonoscapine, aim to overcome the high effective dose requirement. These analogues have been extensively studied, utilising innovative reactions like Cu[I]-catalysed click reactions and Pd [0]-mediated Suzuki coupling to enhance their bioactivity [5,24,86–88].

Efforts continue to improve the anti-neoplastic effects of noscapine. Encapsulation in nanoparticles, the use of antibody–drug conjugates [ADCs] and the development of related compounds are all avenues under exploration [35,71]. While some derivatives have been synthesised, introducing more changes into the noscapine structure remains a viable approach to enhancing its binding affinity with tubulin. The economically viable production of biologically active noscapine is another challenge. The near future will be pivotal in advancing this class of drugs from clinical trials to market introduction, potentially revolutionising cancer treatment by offering cheaper, safer and more potent anticancer agents. These advancements have the potential to significantly reduce the high mortality rate associated with cancer, potentially transforming it into a curable disease [10,24].

In one study [82], molecular docking assays revealed the possibility of in vitro-designed combinatorial therapy against Mpro of SARS-CoV-2. Main protease (Mpro) performs a key biological function in the viral infection and progression of SARS-CoV-2. In silico experiments performed with noscapine–hydroxychloroquine (Nos–Hcq) conjugates revealed their binding affinity with the main protease (Mpro) using molecular dynamics simulation.

13. Conclusions

Noscapine, a natural compound with a history of clinical use as an antitussive dating back to the 1950s, has garnered attention for its diverse pharmacological properties in recent years. Cellular studies have revealed its potential in inducing apoptosis, moderating microtubule dynamics, inhibiting tumour cell proliferation and exerting inhibitory effects on NF-κB, VEGF and EGFR. Additionally, noscapine demonstrates anti-inflammatory properties, substantially reducing the levels of proinflammatory factors like IL-1β, IFN-c, IL-6 and TNF-α. It also acts as an antioxidant by inhibiting NO and diminishing ROS levels. Notably, noscapine not only hampers cancer cell growth but also hinders metastasis to other tissues. Moreover, its ability to traverse the blood–brain barrier allows it to exert effective inhibitory effects on glioblastoma, offering potential therapeutic benefits. Furthermore, cellular studies have demonstrated synergistic effects when noscapine is used in conjunction with conventional anticancer drugs. These therapeutic attributes, coupled with its low systemic toxicity, commendable oral bioavailability and precise tumour targeting capabilities, position noscapine as a promising option for treating various inflammatory disorders and cancers.

Author Contributions: A.P. conceived and designed the review. R.B., M.S. and A.P. co-wrote, edited and revised the draft critically and approved the final version of the manuscript. R.B. and M.S. contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analysed in this study.

Acknowledgments: We would like to thank Dinesh Khattar for allowing us to conduct this research and Labani, a graduate from Department of Zoology, Kirori Mal College, the University of Delhi, for helping with the digital figures.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

Mpro—main protease, SARS-CoV-2—severe acute respiratory syndrome coronavirus, COVID-19—coronavirus disease 2019, NH4OH—ammonium hydroxide, KOH—potassium hydroxide, HCL—hydrochloric acid, Cu—copper, Pd—palladium, ADCs—antibody drug conjugates, NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells, IL-1β—cytokine interleukin-1β, IFN-c—interferon, IL-6—interleukin-6, VEGF—vascular endothelial growth factor, EGFR—estimated glomerular filtration rate, NO—nitric oxide, C13—carbon at the 13th place of the chemical entity, C8—carbon at the 8th place of the chemical entity, JNK—c-Jun N-terminal kinase, HIF-1α—hypoxia-inducible factor-1 alpha, VEGF—vascular endothelial growth factor, NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells, TGF-β—transforming growth factor-beta, Red-Br-Nos—bromonoscapine, PC-3—prostate cancer cell line, DNA—deoxyribonucleic acid, methyl-β-CD—methyl-β-cyclodextrin, GGMs—guar gum microspheres, IC50—half-maximal inhibitory concentration, Br-Nos—bromonoscapine, TNFα—tumour necrosis factor α, CXCL10 C-X-C—motif chemokine 10 protein, IP-10—interferon-gamma-induced protein 10, HeLa—"immortal" cell line used in research, later named "HeLa" after the first two letters of Henrietta Lacks's first and last name, TLR—-oll like receptor, U87/U87MG—Uppsala 87 Malignant Glioma cell line, MCF-7—Michigan Cancer Foundation-7 breast cancer cell line, G2-M—second growth phase and mitosis checkpoint, MDA-MB-231—epithelialtriple negative breast cancer cell line, Bcl-2—B-cell lymphoma-2, NLPs—nanostructured lipid particles, A549—human non-small cell lung cancer cell line. ACE—angiotensin-converting enzyme, rt-PA—recombinant tissue plasminogen activator, FDA—Food and Drug Administration, Bradykinin B-2 receptor—type 2 bradykinin Receptor, NSCLC—non-small cell lung cancer, H460—human non-small cell lung cancer line, Nos—noscapine, Nu mice—nude mice, PARP—poly (ADP-ribose) polymerases, Bax—Bcl-2-associated X protein, TMZ—temozolomide. E. G7-OVA—mouse lymphoma cell line created by introducing a plasmid containing the complete sequence of chicken ovalbumin (OVA) into electroporated EL4 cells, resulting in constitutive OVA synthesis and secretion, TUNEL—terminal deoxynucleotidyl transferase biotindUTP nick end labelling, P53—tumour protein, p21—cyclin-dependent kinase inhibitor 1, HCT 116—human colorectal carcinoma cell line, p13K/mTOR—the phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR) pathway, PTEN—phosphatase and TENsin homolog deleted on chromosome 10, CIS—cisplatin, Nos-ES-GNs—noscapine-loaded estrone-conjugated gelatin nanoparticles, NP (VinPhe-Nos)—a derivative of noscapine, PC12—a type of catecholamine cell, used in neurology and toxicology research generally, PCOS—polycystic ovarian syndrome, HPV—human papillomavirus, FSH—follicle-stimulating hormone, LH—luteinising hormone, RU486—a medication, also known as mifepristone, 99mTc-noscapine—technetium-99m.

References

1. Hogshire, J. *Opium for the Masses: Harvesting Nature's Best Pain Medication*, 2nd ed.; Feral House: Port Townsend, WA, USA, 2009.
2. Chen, X.; Dang, T.; Facchini, P. Noscapine comes of age. *Phytochemistry* **2015**, *111*, 7–13. [CrossRef] [PubMed]
3. Aragón, P.F.; Martínez, F.E.; Márquez, E.C.; Pérez, A.; Mora, R.; Torres, L. *History of Opium*; Elsevier: Amsterdam, The Netherlands, 2002; Volume 1242, pp. 19–21.
4. Macht, D. The history of opium and some of its preparations and alkaloids. *Am. Med. Assoc.* **1915**, *64*, 477–481. [CrossRef]
5. Mishra, R.C.; Gundala, S.R.; Karna, P.; Lopus, M.; Gupta, K.K.; Nagaraju, M.; Hamelberg, D.; Tandon, V.; Panda, D.; Reid, M.D.; et al. Design, synthesis and biological evaluation of di-substituted noscapine analogs as potent and microtubule-targeted anticancer agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2133–2140. [CrossRef] [PubMed]
6. Singh, H.; Singh, P.; Kumari, K.D.S.; Chandra, R. A review on noscapine, and its impact on heme metabolism. *Curr. Drug Metab.* **2013**, *14*, 351–360. [CrossRef] [PubMed]
7. Rida, P.; LiVecche, D.; Ogden, A.; Zhou, J. The noscapine chronicle: A pharmaco-historic biography of the opiate alkaloid family and its clinical applications. *Med. Res. Rev.* **2015**, *35*, 1072–1096. [CrossRef]
8. Bhimwal, T.; Puneet Priyadarshini, A. Understanding Polycystic ovary syndrome in Light of Associated Key Genes. *Egypt J. Med. Hum. Genet.* **2023**, *24*, 38. [CrossRef]
9. Priyadarshani, A. Effects of opium alkaloid, noscapine in RU486 induced experimental model of polycystic ovary syndrome. *Indian J. Biochem. Biophys.* **2022**, *59*, 468–478.

10. Tomar, V.; Kukreti, S.; Prakash, S.; Madan, J.; Chandra, R. Noscapine and its analogs as chemotherapeutic agent: Current updates. *Curr. Top. Med. Chem.* **2017**, *17*, 174–188. [CrossRef]
11. HHenary, M.; Narayana, L.; Ahad, S.; Gundala, S.R.; Mukkavilli, R.; Sharma, V.; Owens, E.A.; Yadav, Y.; Nagaraju, M.; Hamelberg, D.; et al. Novel third-generation water-soluble noscapine analogs as superior microtubule-interfering agents with enhanced antiproliferative activity. *Biochem. Pharmacol.* **2014**, *92*, 192–205. [CrossRef]
12. Madan, J.; Baruah, B.; Nagaraju, M.; Abdalla, M.; Turner, T.; Rangari, V.; Hamelberg, D.; Aneja, R. Molecular cyclo encapsulation augments solubility and improves therapeutic index of brominated noscapine in prostate cancer cells. *Mol. Pharm.* **2012**, *9*, 1470–1480. [CrossRef]
13. Rahmanian-Devin, P.; Baradaran Rahimi, V.; Jaafari, M.; Golmohammadzadeh, S.; Sanei-Far, Z.; Askari, V. Noscapine, an emerging medication for different diseases: A mechanistic review. *Evid.-Based Complement. Altern. Med.* **2021**, *2021*, 8402517. [CrossRef] [PubMed]
14. Dang, T.; Facchini, P. CYP82Y1 is N-methylcanadine 1-hydroxylase, a key noscapine biosynthetic enzyme in opium poppy. *J. Biol. Chem.* **2014**, *289*, 2013–2026. [CrossRef] [PubMed]
15. Dang, T.; Facchini, P. Cloning and characterization of canadine synthase involved in noscapine biosynthesis in opium poppy. *FEBS Lett.* **2014**, *588*, 198–204. [CrossRef] [PubMed]
16. Dang, T.; Chen, X.; Facchini, P. Acetylation serves as a protective group in noscapine biosynthesis in opium poppy. *Nat. Chem. Biol.* **2015**, *11*, 104–106. [CrossRef] [PubMed]
17. Chen, X.; Facchini, P. Short-chain dehydrogenase/reductase catalyzing the final step of noscapine biosynthesis is localized to laticifers in opium poppy. *Plant J.* **2014**, *77*, 173–184. [CrossRef]
18. Dahlström, B.; Mellstrand, T.; Löfdahl, C.; Johansson, M. Pharmakokinetic properties of noscapine. *Eur. J. Clin. Pharmacol.* **1982**, *22*, 535–539. [CrossRef] [PubMed]
19. Mahmoudian, M.; Rahimi-Moghaddam, P. The anti-cancer activity of noscapine: A review. *Recent Pat. Anticancer Drug Discov.* **2009**, *4*, 92–97. [CrossRef] [PubMed]
20. Ye, K.; Zhou, J.; Landen, J.; Bradbury, E.; Joshi, H. Sustained activation of p34 cdc2 is required for noscapine-induced apoptosis. *J. Biol. Chem.* **2001**, *276*, 46697–46700. [CrossRef]
21. Heidari, N.; Goliaei, B.; Moghaddam, P.; Rahbar-Roshandel, N.; Mahmoudian, M. Apoptotic pathway induced by noscapine in human myelogenous leukemic cells. *Anticancer Drugs* **2007**, *18*, 1139–1147. [CrossRef]
22. Pezzuto, A.; Carico, E. Role of HIF-1 in cancer progression: Novel insights. A review. *Curr. Mol. Med.* **2018**, *18*, 343–351. [CrossRef]
23. Porcù, E.; Sipos, A.; Basso, G.; Hamel, E.; Bai, R.; Stempfer, V.; Udvardy, A.; Bényei, A.C.; Schmid hammer, H.; Antus, S.; et al. Novel 9′-substituted-noscapines: Synthesis with Suzuki cross-coupling, structure elucidation and biological evaluation. *Eur. J. Med. Chem.* **2014**, *84*, 476–490. [CrossRef] [PubMed]
24. Tomar, R.; Sahni, A.; Chandra, R. Review of noscapine and its analogues as potential anti-cancer drugs. *Mini-Rev. Org. Chem.* **2018**, *15*, 345–363. [CrossRef]
25. Karna, P.; Zughaier, S.; Pannu, V.; Simmons, R.; Narayana, S.; Aneja, R. Induction of reactive oxygen species-mediated autophagy by a novel microtubule-modulating agent. *J. Biol. Chem.* **2010**, *285*, 18737–18748. [CrossRef] [PubMed]
26. Pannu, V.; Rida, P.C.G.; Ogden, A.; Clewley, R.; Cheng, A.; Karna, P.; Lopus, M.; Mishra, R.C.; Zhou, J.; Aneja, R. Induction of robust de novo centrosome amplification, high-grade spindle multipolarity and metaphase catastrophe: A novel chemotherapeutic approach. *Cell Death Dis.* **2012**, *3*, e346. [CrossRef]
27. Madan, J.; Gundala, S.R.; Baruah, B.; Nagaraju, M.; Yates, C.; Turner, T.; Rangari, V.; Hamelberg, D.; Reid, M.D.; Aneja, R. Cyclodextrin complexes of reduced bromonoscapine in guar gum microspheres enhance colonic drug delivery. *Mol. Pharm.* **2014**, *11*, 4339–4349. [CrossRef]
28. Naik, P.; Santoshi, S.; Rai, A.; Joshi, H. Molecular modeling and competition binding study of Br-noscapine and colchicine provides insight into noscapinoid-tubulin binding site. *J. Mol. Graph Model.* **2011**, *29*, 947–955. [CrossRef]
29. Zughaier, S.; Karna, P.; Stephens, D.; Aneja, R. Potent anti-inflammatory activity of novel microtubule-modulating brominated noscapineanalogs. *PLoS ONE* **2010**, *5*, e9165. [CrossRef]
30. DeBono, A.J.; Mistry, S.J.; Xie, J.; Muthiah, D.; Phillips, J.; Ventura, S.; Callaghan, R.; Pouton, C.W.; Capuano, B.; Scammells, P.J. The synthesis and biological evaluation of multifunctionalised derivatives of noscapine as cytotoxic agents. *Chem. Med. Chem.* **2014**, *9*, 399–410. [CrossRef]
31. Zhou, J.; Gupta, K.; Aggarwal, S.; Aneja, R.; Chandra, R.; Panda, D.; Joshi, H.C. Brominated derivatives of noscapine are potent microtubule-interfering agents that perturb mitosis and inhibit cell proliferation. *Mol. Pharmacol.* **2003**, *63*, 799–807. [CrossRef]
32. Verma, A.K.; Bansal, S.; Singh, J.; Tiwari, R.K.; Sankar, V.K.; Tandon, V.; Chandra, R. Synthesis and in vitro cytotoxicity of haloderivatives of noscapine. *Bioorg. Med. Chem.* **2006**, *14*, 6733–6736. [CrossRef]
33. Aneja, R.; Miyagi, T.; Karna, P.; Ezell, T.; Shukla, D.; Vij Gupta, M.; Yateset, C.; Chinni, S.R.; Zhau, H.; Chung, L.W.K.; et al. A novel microtubule-modulating agent induces mitochondrially driven caspase dependent apoptosis via mitotic checkpoint activation in human prostate cancer cells. *Eur. J. Cancer* **2010**, *26*, 1668–1678. [CrossRef]
34. Pannu, V.; Karna, P.; Sajja, H.; Shukla, D.; Aneja, R. Synergistic antimicrotubule therapy for prostate cancer. *Biochem. Pharmacol.* **2011**, *81*, 478–487. [CrossRef] [PubMed]

35. Madan, J.; Pandey, R.; Jain, V.; Katare, O.; Chandra, R.; Katyal, A. Poly (ethylene)-glycol conjugated solid lipid nanoparticles of noscapinemprove biological half-life, brain delivery and efficacy in glioblastoma cells. *Nanomed. Nanotechnol. Biol. Med.* **2013**, *9*, 492–503. [CrossRef] [PubMed]
36. Qi, Q.; Liu, X.; Li, S.; Joshi, H.; Ye, K. Synergistic suppression of noscapine and conventional chemotherapeutics on human glioblastoma cell growth. *ActaPharmacol. Sin.* **2013**, *34*, 930–938. [CrossRef]
37. Altinoz, M.; Bilir, A.; Del Maestro, R.; Tuna, S.; Ozcan, E.; Gedikoglu, G. Noscapine and diltiazem augment taxol and radiation-induced S-phase arrest and clonogenic death of C6 glioma in vitro. *Surg Neurol.* **2006**, *65*, 478–485. [CrossRef] [PubMed]
38. Jhaveri, N.; Cho, H.; Torres, S.; Wang, W.; Schönthal, A.H.; Petasis, N.A.; Louie, S.G.; Hofman, F.M.; Chen, T.C. Noscapine inhibits tumor growth in TMZ-resistant gliomas. *Cancer Lett.* **2001**, *312*, 245–252. [CrossRef]
39. Erguven, M.; Bilir, A.; Yazihan, N.; Ermis, E.; Sabanci, A.; Aktas, E.; Aras, Y.; Alpman, V. Decreased therapeutic effects of noscapine combined with imatinibmesylate on human glioblastoma in vitro and the effect of midkine. *Cancer Cell Int.* **2011**, *11*, 18. [CrossRef]
40. Jyoti, K.; Kaur, K.; Pandey, R.; Jain, U.; Chandra, R.; Madan, J. Inhalable nanostructured lipid particles of 9-bromo-noscapine, a tubulin-binding cytotoxic agent: Invitro and in vivo studies. *J. Colloid Interface Sci.* **2015**, *455C*, 219–230. [CrossRef]
41. Ebrahimi, S.; Zareie, M.; Rostami, P.; Mahmoudian, M. Interaction of noscapine with the bradykinin mediation of the cough response. *Acta Physiol. Hung.* **2003**, *90*, 147–155. [CrossRef]
42. Mooraki, A.; Jenabi, A.; Jabbari, M.; Zolfaghari, M.I.; Javanmardi, S.Z.; Mahmoudian, M.; Bastani, B. Noscapine suppresses angiotensin converting enzyme inhibitors-induced cough. *Nephrology* **2005**, *10*, 348–350. [CrossRef]
43. Chandra, R.; Madan, J.; Singh, P.; Chandra, A.; Kumar, P.; Tomar, V.; Dass, S.K. Implications of nanoscale based drug delivery systems in delivery and targeting tubulin binding agent, noscapine in cancer cells. *Curr. Drug Metab.* **2012**, *13*, 1476–1483. [CrossRef]
44. Altinoz, M.; Guloksuz, S.; Ozpinar, A. Immunomodifying and neuroprotective effects of noscapine: Implications for multiple sclerosis, neurodegenerative, and psychiatric disorders. *Chem. Biol. Interact.* **2022**, *352*, 109794. [CrossRef] [PubMed]
45. Segal, M.S.; Goldstein, M.M.; Attinger, E.O. The use of noscapine (narcotine) as an antitussive agent. *Dis. Chest* **1957**, *32*, 305–309. [CrossRef] [PubMed]
46. Mahmoudian, M.; Rezvani, M.; Rohani, M.; Benaissa, F.; Jalili, M.; Ghourchian, S. A novel effect of Noscapine on patients with massive ischemic stroke: A pseudo-randomized clinical trial. *Iran J. Neurol.* **2015**, *14*, 12. [PubMed]
47. Ye, K.; Ke, Y.; Keshava, N.; Shanks, J.; Kapp, J.; Tekmal, R.; Petros, J.; Joshi, H.C. Opium alkaloid noscapine is an antitumor agent that arrests metaphase and induces apoptosis in dividing cells. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1601–1606. [CrossRef]
48. Zhou, J.; Panda, D.; Landen, J.; Wilson, L.; Joshi, H. Minor alteration of microtubule dynamics causes loss of tension across kinetochore pairs and activates the spindle checkpoint. *J. Biol. Chem.* **2002**, *277*, 17200–17208. [CrossRef]
49. Jackson, T.; Chougule, M.; Ichite, N.; Patlolla, R.; Singh, M. Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. *CancerChemother. Pharmacol.* **2008**, *63*, 117–126. [CrossRef]
50. Li, S.; He, J.; Cao, G.; Tang, S.; Tong, Q.; Joshi, H. Noscapine induced apoptosis via downregulation of survivin in human neuroblastoma cells having wild type or null p53. *PLoS ONE* **2012**, *7*, e40076. [CrossRef]
51. Chougule, M.; Patel, A.; Sachdeva, P.; Jackson, T.; Singh, M. Enhanced anticancer activity of gemcitabine in combination with noscapine via antiangiogenic and apoptotic pathway against non-small cell lung cancer. *PLoS ONE* **2011**, *6*, e27394. [CrossRef]
52. Madan, J.; Pandey, R.; Jain, U.; Katare, O.; Katyal, A. Sterically stabilized gelatin microassemblies of noscapine enhance cytotoxicity, apoptosis and drug delivery in lung cancer cells. *Colloids Surf. B Biointerfaces* **2013**, *107*, 235–244. [CrossRef]
53. Chougule, M.; Patel, A.; Sachdeva, P.; Jackson Singh, M. Anticancer activity of noscapine, an opioid alkaloid in combination with cisplatin in human non-small cell lung cancer. *Lung Cancer* **2011**, *71*, 271–282. [CrossRef] [PubMed]
54. Ivanenkov, Y.A.; Filyaeva, K.Y.; Matniyazov, R.T.; Baymiev, A.K.; Baymiev, A.K.; Vladimirova, A.A.; Yamidanov, R.S.; Mavzyutov, A.R.; Zileeva, Z.R.; Zainullina, L.F.; et al. Antibacterial activity of noscapine analogs. *Bioorg. Med. Chem. Lett.* **2021**, *43*, 128055. [CrossRef] [PubMed]
55. Shen, W.; Liang, B.; Yin, J.; Li, X.; Cheng, J. Noscapine increases the sensitivity of drug-resistant ovarian cancer cell line SKOV3/DDP to cisplatin by regulating cell cycle and activating apoptotic pathways. *Cell Biochem. Biophys.* **2014**, *72*, 203–213. [CrossRef] [PubMed]
56. Zhou, J.; Gupta, K.; Yao, J.; Ye, K.; Panda, D.; Giannakakou, P.; Joshi, H.C. Paclitaxel-resistant human ovarian cancer cells undergo c-Jun NH2-terminal kinase-mediated apoptosis in response to noscapine. *J. Biol. Chem.* **2002**, *277*, 39777–39785. [CrossRef] [PubMed]
57. Su, W.; Huang, L.; Ao, Q.; Zhang, Q.; Tian, X.; Fang, Y.; Lu, Y. Noscapine sensitizes chemoresistant ovarian cancer cells to cisplatin through inhibition of HIF-1alpha. *Cancer Lett.* **2011**, *305*, 94–99. [CrossRef]
58. Nisar, S.; Masoodi, T.; Prabhu, K.S.; Kuttikrishnan, S.; Zarif, L.; Khatoon, S.; Ali, S.; Uddin, S.; Akil, A.A.; Singh, M.; et al. Natural products as chemo-radiation therapy sensitizers in cancers. *Biomed. Pharmacother.* **2022**, *154*, 113610. [CrossRef] [PubMed]
59. Aneja, R.; Vangapandu, S.; Lopus, M.; Chandra, R.; Panda, D.; Joshi, H. Development of a novel nitro-derivative of noscapine for the potential treatment of drug-resistant ovarian cancer and T-cell lymphoma. *Mol. Pharmacol.* **2006**, *69*, 1801–1809. [CrossRef]
60. Newcomb, E.; Lukyanov, Y.; Alonso-Basanta, M.; Esencay, M.; Smirnova, I.; Schnee, T.; Shao, Y.; Devitt, M.L.; DavidZagzag, M.D.; McBride, W.; et al. Antiangiogenic effects of noscapine enhance radioresponse for GL261 tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **2008**, *71*, 1477–1484. [CrossRef]

61. Tormoehlen, L.; Pascuzzi, R. Thymoma, myasthenia gravis, and other paraneoplastic syndromes. *Hematol. Oncol. Clin. N. Am.* **2008**, *22*, 509–526. [CrossRef]
62. Liu, M.; Luo, X.; Liao, F.; Lei, X.; Dong, W. Noscapine induces mitochondria mediated apoptosis in gastric cancer cells in vitro and in vivo. *Cancer Chemother. Pharmacol.* **2011**, *67*, 605–612. [CrossRef]
63. Nourbakhsh, F.; Askari, V. Biological and pharmacological activities of noscapine: Focusing on its receptors and mechanisms. *BioFactors* **2021**, *47*, 975–991. [CrossRef]
64. Aneja, R.; Ghaleb, A.; Zhou, J.; Yang, V.; Joshi, H. p53 and p21 determine the sensitivity of noscapine-induced apoptosis in colon cancer cells. *Cancer Res.* **2007**, *67*, 3862–3870. [CrossRef]
65. Ogino, S.; Nosho, K.; Shima, K.; Baba, Y.; Irahara, N.; Kirkner, G.J.; Hazra, A.; De Vivo, I.; Giovannucci, E.L.; Meyerhardt, J.A.; et al. p21 expression in colon cancer and modifying effects of patient age and body mass index on prognosis. *Cancer Epidemiol. Biomark. Prev.* **2009**, *18*, 2513–2521. [CrossRef] [PubMed]
66. Hollstein, M.; Sidransky, D.; Vogelstein, B.; Harris, C.C. p53 mutations in human cancers. *Science* **2010**, *253*, 49–53. [CrossRef] [PubMed]
67. McBride, O.W.; Merry, D.; Givol, D. Gene for human p53 cellular tumor antigen is located on chromosome 17 short arm (17p13). *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 130–134. [CrossRef] [PubMed]
68. Tian, X.; Liu, M.; Zhu, Q.; Tan, J.; Liu, W.; Wang, Y.; Chen, W.; Zou, Y.; Cai, Y.; Han, Z.; et al. Down-regulation of liver-intestine cadherin enhances noscapine-induced apoptosis in human colon cancer cells. *Expert Rev. Anticancer Gerapy.* **2017**, *17*, 857–863. [CrossRef] [PubMed]
69. Yang, Z.; Liu, M.; Peng, X.; Lei, X.; Zhang, J.; Dong, W. Noscapine induces mitochondria-induced apoptosis in human colon cancer cells in vivo and in vitro. *Biochem. Biophys. Res. Commun.* **2012**, *421*, 627–633. [CrossRef]
70. Chougule, M.; Patel, A.; Jackson, T.; Singh, M. Antitumor activity of noscapine in combination with doxorubicin in triple negative breast cancer. *PLoS ONE* **2011**, *6*, e17733. [CrossRef]
71. Madan, J.; Gundala, S.R.; Kasetti, Y.; Bharatam, P.V.; Aneja, R.; Katyal, A.; Jain, U.K. Enhanced noscapine delivery using estrogen-receptor-targeted nanoparticles for breast cancer therapy. *Anticancer Drugs* **2014**, *25*, 704–716. [CrossRef]
72. Sammeta, S.M.; Wang, L.; Mutyam, S.K. Formulation approaches to improving the delivery of an antiviral drug with activity against seasonal flu. *Pharm. Devel.-Opment. Technol.* **2015**, *20*, 169–175. [CrossRef]
73. Cheriyamundath, S.; Mahaddalkar, S.; Kantevari, S.; Lopus, M. Induction of acetylation and bundling of cellular microtubules by 9-(4-vinylphenyl) noscapine elicits S-phase arrest in MDA-MB-231 cells. *Biomed. Pharm.-Ther.* **2017**, *86*, 74–80. [CrossRef]
74. Nambiar, N.; Nagireddy, P.K.R.; Pedapati, R.; Kantevari, S.; Lopus, M. Tubulin- and ROS-dependent anti- proliferative mechanism of a potent analogue of noscapine, N-propargylnoscapine. *Life Sci.* **2020**, *258*, 118238. [CrossRef]
75. Barken, I.; Geller, J.; Rogosnitzky, M. Noscapine inhibits human prostate cancer progression and metastasis in a mouse model. *Anticancer Res.* **2008**, *28*, 3701–3704.
76. Shin, J.; Lee, S.; Lee, M. Inhibitory effects of noscapine on dopamine biosynthesis in PC12 cells. *Arch. Pharm. Res.* **1997**, *20*, 510–512. [CrossRef] [PubMed]
77. Priyadarshini, A.; Chuttani, K.; Mittal, G.; Bhatnagar, A. Radiolabeling, biodistribution and gamma scintigraphy of noscapine hydrochloride in normal and polycystic ovary induced rats. *J. Ovarian Res.* **2010**, *3*, 10. [CrossRef] [PubMed]
78. Matthews, J.; Morgan, R.; Sleigher, C.; Frey, T. Do viruses require the cytoskeleton? *Virol. J.* **2013**, *10*, 121–125. [CrossRef] [PubMed]
79. Kumar, N.; Sood, D.; van der Spek, P.J.; Sharma, H.S.; Chandra, R. Molecular binding mechanism and pharmacology comparative analysis of noscapine for repurposing against SARS-CoV-2 protease. *J. Proteome Res.* **2020**, *19*, 4678–4689. [CrossRef]
80. Barati, S.; Feizabadi, F.; Khalaj, H.; Sheikhzadeh, H.; Jamaati, H.R.; Farajidavar, H.; Dastan, F. Evaluation of noscapine-licorice combination effects on cough relieving in COVID-19 outpatients: A randomized controlled trial. *Front. Pharmacol.* **2023**, *14*, 1102940. [CrossRef]
81. Kumar, D.; Kumari, K.; Jayaraj, A.; Kumar, V.; Kumar, R.V.; Dass, S.K.; Chandra, R.; Singh, P. Understanding the binding affinity of noscapines with protease of SARS-CoV-2 for COVID-19 using MD simulations at different temperatures. *J. Biomol. Struct. Dyn.* **2021**, *39*, 2659–2672. [CrossRef]
82. Kumar, N.; Awasthi, A.; Kumari, A.; Sood, D.; Jain, P.; Singh, T.; Sharma, N.; Grover, A.; Chandra, R. Antitussive noscapine and antiviral drug conjugates as arsenal against COVID-19: A comprehensivechemoinformatics analysis. *J. Biomol. Struct. Dyn.* **2022**, *40*, 101–116. [CrossRef]
83. Winter, C.; Flataker, L. Toxicity studies on noscapine. *Toxicol. Appl. Pharmacol.* **1961**, *3*, 96–106. [CrossRef] [PubMed]
84. Mitchell, I.; Carlton, J.; Chan, M.; Robinson, A.; Sunderland, J. Noscapine-induced polyploidy in vitro. *Mutagenesis* **1991**, *6*, 479–486. [CrossRef] [PubMed]
85. Sneyd, J. Papaveretum in women of childbearing potential. *Brit. Med. J.* **1991**, *303*, 852. [CrossRef] [PubMed]
86. Cao, J.F.; Gong, Y.; Wu, M.; Yang, X.; Xiong, L.; Chen, S.; Xiao, Z.; Li, Y.; Zhang, L.; Zan, W.; et al. Exploring the mechanism of action of licorice in the treatment of COVID-19 through bioinformatics analysis and molecular dynamics simulation. *Front. Pharmacol.* **2022**, *13*, 1003310. [CrossRef]

87. Verma, A.; Jha, R.R.; Chaudhary, R.; Tiwari, R.; Danodia, A.K. 2-(1-Benzotriazolyl) pyridine: A Robust Bidentate Ligand for the Palladium-Catalyzed C C (Suzuki, Heck, Fujiwara–Moritani, Sonogashira), C N and C S Coupling Reactions. *Adv. Synth. Catal.* **2013**, *355*, 421–438. [CrossRef]
88. Manchukonda, N.; Naik, P.; Sridhar, B.; Kantevari, S. Synthesis and biological evaluation of novel biaryl type alpha-noscapine congeners. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5752–5757. [CrossRef]