Noscapine, an opium alkaloid, acts as a budding therapeutic agent for various disease conditions: A systematic review

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Abstract: Noscapine, a naturally occurring alkaloid obtained from opium poppies, has been used as an antitussive since the 1950s. Euphoria and addiction are not its effects. Several studies have demonstrated that noscapine has strong anti-inflammatory properties. It boosts antioxidant defences by lowering reactive oxygen species and nitric oxide metabolites and raising glutathione levels. Noscapine has been shown in recent research to possess antiviral properties that effectively stop the spread of viruses like human rhinovirus, respiratory syncytial virus, and some influenza strains. Additionally, noscapine's immunomodulatory properties have been demonstrated, indicating that it might be useful in managing viral infection. Research indicates that noscapine has strong antimalarial properties because it inhibits FP2, a protein essential to the malaria parasite's survival. This disruption prevents the parasite from breaking down heme, which ultimately leads to toxic accumulation and death. Noscapine has the potential to cure cerebral stroke and ischemic damage because it decreases the overexpression of bradykinin B1 and B2 receptors, which in turn reduces vascular permeability and nerve damage. Additionally, it promotes reperfusion at the site of ischemia, suggesting possible therapeutic benefits. In summary, noscapine is a flexible and diverse drug with a wide range of therapeutic uses. This study aims to provide insights into this treatment approach and to illuminate possible mechanisms via which noscapine combats different disorders.

Keywords: Noscapine, Pharmacokinetics; Antitussive; Antiviral; Antimalarial.

INTRODUCTION

A wide range of nutrients is necessary for the human body to function at its best and maintain excellent health. In addition to essential nutrients like vitamins and minerals, many foods also have non-nutritional ingredients that have been shown to prevent degenerative diseases like cancer [1]. These substances belong to a broad class of molecules known as phytochemicals, which also comprises vitamins such as carotenoids and dietary polyphenols, flavonoids, alkaloids, phenolic acids, sulfur-rich compounds, and flavonoid-rich compounds [2,3]. Natural alkaloids are organic compounds that are made up of one or more basic nitrogen atoms grouped in a heterocyclic ring [4-6]. They are distributed widely over the kingdom of plants, with the largest concentrations occurring in the families Leguminosae, Neisseriaceae, Ranunculaceae, Loganiaceae, and Papaveraceae [7,8]. Alkaloids are a useful resource for drug discovery because of their diverse biological roles, including the capacity to fight malaria, reduce inflammation, fight cancer, and offer analgesia [9-12]. Research indicates that alkaloids obtained from plants can stop the spread of cancer by altering key signalling pathways linked to the cell cycle, metastasis, and proliferation [13]. Two examples of clinical anticancer medications based on alkaloids are vinblastine and vincristine [14]. Noscapine, a benzyl isoquinoline alkaloid, is one of the many alkaloids. It is typically extracted from plants that have a high alkaloid content, such papaverine [15]. Noscapine has the unique virtue of not producing euphoria, addiction, or respiratory suppression like other medicines made from poppy plants [16]. It is a safer option for medicinal purposes because it can be used to treat a wide range of disorders without running the risk of negatively affecting the central nervous system [17]. Although noscapine has mild effects on the central nervous system, it has been demonstrated to have several potential therapeutic benefits. It has been used, for instance, to treat coughs due to its mild suppressant properties. Its anticancer properties have also been shown, indicating that it might be a useful addition to cancer treatment regimens. Noscapine has been associated with the possibility of being a powerful anticancer medication due to its ability to inhibit microtubule activity, which is required for cell

division and proliferation [18-20]. More investigation is still required to completely explore the range of potential advantages of noscapine.

1. Physico-chemical properties and Pharmacokinetics of Noscapine

1.1. Physico-chemical properties-

Noscapine is an alkaloid found in Papaver somniferum, also known as opium poppy. It is the second most prevalent plant alkaloid, behind morphine [21,22]. Noscapine weighs 413.42 g/mol and has the chemical formula $C_{22}H_{23}NO_7$. It is a polar molecule with a density of 1.395 g/mL and a melting point of 176°C. This white powder tastes bitter and has no fragrance. In water, noscapine is mostly insoluble but easily soluble in vegetable oils, acetone, and benzene. It is also slightly soluble in alcohol and ether [23,24]. On the other hand, ethanol and water can easily dissolve noscapine hydrochloride. Urine excretes meconin, a stable noscapine metabolite. The rate at which meconin dissolves in water at 25°C is 2.5 mg/ml. But it's essential to keep in mind that meconin causes skin irritation [24]. Noscapine can easily cross the blood-brain barrier (BBB) as it has high lipophilicity. This property makes the drug potentially useful in treating some neurological diseases [25,26]. More research is required to determine its efficacy as a medicinal agent.

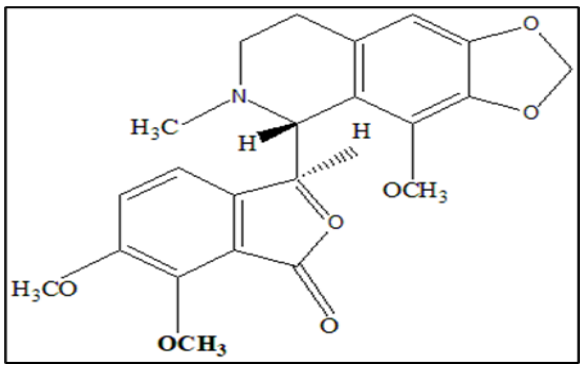

Fig 1: Noscapine ($C_{22}H_{23}NO_7$)

1.2. Pharmacokinetics-

A study under consideration focused on the pharmacokinetic study and ADMET predictions of noscapine compounds, namely D3, D4, and D6 [27]. The study found that these compounds exhibit high levels of human intestinal absorption, with values ranging from 91.997% to 95.957%, indicating excellent absorption rates. The GI solubility of noscapine compounds was found to be over 90%, which is crucial in determining the handling and formulation of the drug and ensuring efficient drug delivery to the target. Additionally, the study predicted the blood-brain barrier (BBB) permeability (log BB) and central nervous system permeability for these compounds, with values ranging from -1.066 to -1.406 and -2.433 to -3.192, respectively [28,29]. The study found that noscapine derivatives had Log BB above -1, indicating that these derivatives are better distributed to the brain, with Log PS above -2. This implies that these compounds are likely to penetrate the central nervous system more efficiently [29]. Furthermore, the study examined the role of cytochrome isoenzymes, with a particular focus on the 3A4 family, in the metabolism of the novel noscapine compounds. The study found that members of the 3A4 family acted as both substrates and inhibitors of these compounds, making them crucial in drug metabolism [30,31]. Finally, the study examined the total clearance values of these compounds. The total clearance values were found to be within the permissible limit of a drug molecule in the body, indicating that the selected compounds are likely to be cleared from the body efficiently and without adverse effects [32,33].

The pharmacokinetic study conducted focused on comparing the bioavailability of the Nos HCl extrudate formulation with the Nos solution [34]. The study revealed that the Nos HCl extrudate formulation showed a significant increase in AUC, which suggested that the bioavailability of the drug was significantly enhanced by the extrusion method along with an approach to pH modification [34]. The study also found that the stabilization of hydroxypropyl methylcellulose is self-emulsified by solid dispersible carriers of Nos was effective in enhancing the bioavailability of Nos HCl [35]. The study also developed stable self-micro emulsifying dispersions (SMEDDs) as effective carriers for Nos HCl. The SMEDDs were developed using an oil, surfactant or co-surfactant mixture of the Labrafil, Tween-80, and Labrasol which are optimized at a weight ratio of 62.8:9.30:27.90% [36-38]. The study of pharmacokinetics revealed that Mann-Nos SESD, mannosylated noscapine self-emulsifying solid dispersion, increased the bioavailability by 40% more as compared to Nos self-emulsifying solid dispersible microparticles [34]. This study concluded that the Mann-Nos SESDs effectively sensitized the SP cells to cisplatin in vitro and also in an orthotopic lung tumor model of SP origin. The Mann-Nos SESDs also enhanced the antineoplastic effect of chemotherapy based on cisplatin in cisplatin-resistant non-small-cell lung cancer. Moreover, the study reported that hot melt extrusion (HME) was effective in enhancing the bioavailability of various drugs with solid dispersion

technique and pH modifier approach [34]. The study also demonstrated that the drug release of Nos HCl can be enhanced in a basic pH environment while achieving sustained drug release with enhanced bioavailability. In summary, the study provides useful insights into the bioavailability of Nos HCl and its potential carriers, such as SMEDDs and Mann-Nos SESDs, for effective delivery of the drug. The study also sheds light on the effectiveness of HME in enhancing the bioavailability of various drugs [34].

2. Various pharmacological properties of benzyl iso-quinoline alkaloid Noscapine:

Most commonly, noscapine, an opium alkaloid, is used as an antitussive drug. Several other pharmacological properties have also been found to exist in it, such as antiviral, antimalarial, and anticancer activities. Its immunomodulatory actions and ability to act as a microtubule-stabilizing agent further bolster its anticancer potential. Overall, there is a wide range of potential therapeutic applications for noscapine.

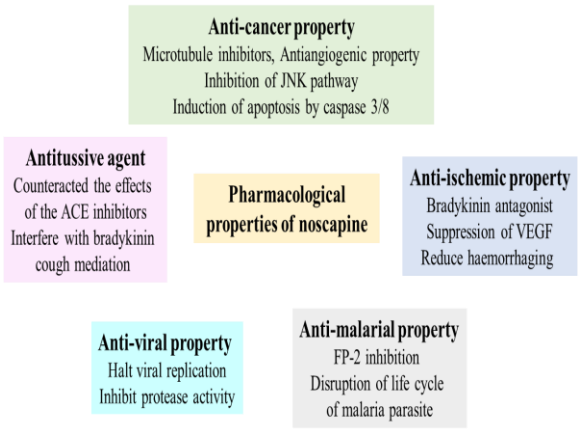

Fig 2: Mechanism of action of noscapine in different diseased condition

2.1: Antitussive agent-

Noscapine is an alkaloid that was discovered in 1930 to have antitussive properties; while the FDA has not approved it for any use, several international regulatory bodies have approved it to treat cough [39]. One of the main benefits of noscapine is that it is not addictive and doesn't have any noticeable sedative, hypnotic, euphoric, or analgesic effects; in contrast, codeine can be abused due to the qualities of its metabolite, codeine-6-glucuronide, which has these properties [40]. One study found that noscapine's antitussive effects diminished in a dose-dependent manner when the receptor of the σ-opioid was antagonistic. This research suggests that noscapine can't bind to the receptor of μ-opioid, in contrast to stronger, more addictive opioids like morphine and codeine. Coughing is a common side effect of ACE inhibitors; noscapine is very effective at suppressing coughing [41,42]. One study found that noscapine reverses the ileal constriction caused by bradykinin in guinea pigs [43]. Bradykinin may result in mucus production and bronchoconstriction, both of which may lead to dry cough. This is avoided with ACE inhibitors [44]. By mitigating the effects of bradykinin receptor activation in the airways, noscapine lessens coughing [45]. In a different study, 90% of patients with a severe ACEI-induced cough responded well to noscapine, recovering fully within 10 days. In guinea pigs treated with captopril and enalapril for seven days, the cough response was made worse by ten milligrams per kilogram of a non-peptide bradykinin B2 receptor agonist [46,47]. Noscapine, at dosages of 0.5, 1 and 2 mg/kg, counteracted the effects of the ACEI and non-peptide agonist. Naloxone, a specific opioid receptor inhibitor, did not prevent the antitussive effects of noscapine in guinea pigs administered enalapril or non-peptide agonists. This suggests that rather than acting through the ε, κ, or δ opioid receptors, noscapine's antitussive activity is mediated by interfering with the bradykinin cough mediation [43]. All things considered, noscapine is a very effective antitussive with negligible side effects, which makes it a good cough treatment choice.

2.2: Noscapine is protective against ischemic injury-

Ischemic damage can have an impact on the body's organs, and studies have shown that bradykinin B1 and B2 receptors are critical to this process [48,49]. While bradykinin B2 receptors are routinely expressed in the central nervous system (CNS), bradykinin B1 receptors are activated in response to the inflammatory cytokines [50,51]. Following ischemic injury, rats' B2 receptors become active, releasing free radicals that have the capacity to damage brain tissue [52]. Nevertheless, it has been found that noscapine, a noncompetitive antagonist of bradykinin receptors, possesses anti-inflammatory and protective qualities that reduce anxiety and brain damage associated with ischemia [53]. It rapidly passes through the blood-brain barrier and has been shown to reduce oedema in neonatal mice against hypoxia and ischemia [54]. Noscapine minimizes damage to muscle function and cell death by inhibiting oxidative stress and reducing neutrophil permeability, among other mechanisms, according to more research [55]. Additionally, it lessens the vascular endothelium's permeability to nerve damage and enhances reperfusion at the location of ischemic injury [56]. Clinical trials have shown that

giving hypoxic-ischemic patients oral noscapine (50 mg/day for seven days) improves their clinical prognosis and dramatically lowers their death rates. In stroke patients, it also improved prognosis and decreased death, albeit the precise mechanism of action is yet unknown [57]. Overall, in a variety of tissue ischemia/reperfusion injury models, bradykinin receptor antagonist Noscapine has demonstrated protective effects, especially in the kidney and brain.

2.3: Antiviral property-

As per the latest research, noscapine might have antiviral properties, namely against respiratory viruses including influenza and respiratory syncytial virus (RSV) [58]. Viral gene expression suppression and viral replication inhibition are assumed to be part of the mechanism of action [59]. According to a study by Matthews et al., noscapine was found to be unsuccessful in preventing the reproduction of three different virus families. The implication is that viruses might not even require a functional cytoskeleton to replicate; they might be able to do so through alternative mechanisms even in circumstances where their usual replication process is disrupted [60]. As noscapine fails to halt viral replication, stronger antivirals are needed to combat cancer-causing viruses such as the human papillomavirus [61]. There appears to be promising evidence, according to a recent investigation, that the naturally occurring alkaloid noscapine can combat SARS-CoV-2. Noscapine targets the binding pocket-3 of the main protease (Mpro) enzyme, which is necessary for the virus to reproduce [62]. The study reported that noscapine bound to Mpro with extreme stability; the RMSD value varied from 0.1 to 1.9 Å, and the RMSF showed peak conformational changes at residues 202 to 306. These binding findings were also strongly correlated with the pharmacokinetic properties of antiviral drugs [63]. It was discovered that erythro-noscapines exhibited a robust binding affinity for the nsP3 protease of CHIKV (PDB ID: 3GPO) and could form a stable complex with the virus's 109-nsP3 protease [65]. 109 demonstrated better interaction through docking than other compounds reported by other research groups. The antiviral Erythro-noscapines' pharmacokinetic characteristics were assessed by calculating the parameters for the Lipinski "Rule of Five" and the bioactivity score [64]. Using molecular dynamics simulations and binding free energy estimates, the likely noscapine-nsP3 protease of CHIKV was identified. Erythro-noscapines may be useful as a medication to treat CHIKV, per the study [65]. The present global epidemic is caused by the new coronavirus COVID-19. Its genome is composed of positive-sense single-stranded RNA, which codes for the poly-protein [66]. Researchers have looked into using noscapine derivatives to limit COVID-19 main protease activity as a possible therapeutic target. The results of the study show that noscapine derivatives had a higher binding affinity than fourteen well-known antiviral drugs, including chloroquine and hydroxychloroquine. The top six were further refined to identify the most potent noscapine derivative. The investigation's findings suggest that noscapine derivatives could be used to treat COVID-19 [67].

2.4: Antimalarial properties-

The significance of the protein FP-2 in the life cycle of parasites has been shown, particularly in the maturation phase [68]. Researchers believe that FP-2 inhibition would be a useful target for the creation of new antimalarial drugs because it has been demonstrated to be an effective method of postponing the production of parasites [69]. Strangely, noscapine has been a common antimalarial drug for many years. The usage of noscapine for this purpose began with the suggestion of Sir Robert Williams, a member of the Royal Commission on Opium from 1893 to 1895 [70]. The effectiveness of noscapine as an antimalarial drug was assessed further through the use of both in vitro and in vivo testing. This entailed utilizing P. berghei ANKA, P. falciparum 3D7, and P. falciparum clinical isolate Pf140/SS to compare Noscapine to traditional Dihydro artemisinin (DHA) [71]. In this work, the antimalarial activity of a naturally occurring phytochemical compound termed noscapine was evaluated against the Plasmodium falciparum 3D7 strain (Pf3D7), the clinical isolate Pf140/SS, and the Plasmodium berghei ANKA (PbA) [72]. The study found that noscapine had potent antimalarial action against Pf3D7 and Pf140/SS, with IC50 values of 7.68±0.88 and 5.57±0.74 nM/mL, respectively. These values were similar to those of the traditional antimalarial medication, dihydro artemisinin (DHA). Furthermore, noscapine was able to reduce over 95% of PbA-infected Wister albino rats after a 4-day test. Importantly, noscapine did not exhibit any toxicity or haemolysis even at high dosages. This study suggests that noscapine could be utilized to make antimalarial drugs [72]. A recent study examined the stability and binding affinity of noscapine for the FP-2 protein, which may be a target for the creation of inhibitors against various diseases, including cancer and malaria [73]. Molecular simulation methods were used in the study to compare the kinetics and structural alterations of Noscapine to those of other drugs, such as Reticuline, Aclidinium, and the reference drug Artemisinin [74]. After a 50 ns simulation run, the results indicated that Noscapine exhibited a stable and

equilibrated system with minimal conformational changes in the protein structure, indicating a strong contact with the FP-2 protein's residues. It was found that noscapine had a higher binding affinity than other systems, indicating that it might be a viable option for the future development of novel FP-2 inhibitors [75]. Further analysis revealed that the combination of FP-2-Noscapine was less accessible to that of water molecules than other systems, indicating that the binding of noscapine is independent of the water molecules' accessibility in the FP-2 active site. The residues in the FP-2-Reticuline system are more flexible, which suggests that they participate less in binding to the protein [73]. Moreover, an interaction analysis revealed that both the noscapine and reticuline bind to the same amino acid residues on the FP-2 protein (TRP206 and ALA157) as artemisinin, indicating that the latter may be repurposed for antimalarial action [73]. Additionally, noscapine has strong anticancer qualities that could be used to develop new antimalarial drugs. Because of this, the study provides valuable information about the potential of noscapine as a workable alternative for producing novel FP-2 inhibitors that might be utilized to treat a variety of diseases, including cancer and malaria [73].

2.5: Anticancer properties-

Numerous investigations have indicated that the drug noscapine can impede the growth of diverse cancer cells, even those that are resistant to drugs, while maintaining the integrity of healthy cells [74]. Substances that block microtubules can activate the mitotic phase control station, which stops the cell cycle and keeps the ratio of monomer to tubulin polymer in balance [75]. Numerous studies have reported that noscapine shows inhibitory effects on a variety of cancer types, including ovarian, skin, blood, breast, lung, and glioblastoma. It has also not demonstrated toxicity in a dose-dependent manner to the tumor cells of the kidney, heart, liver, bone marrow, spleen, or small intestine [24]. A recent study detected the anti-proliferative effect of noscapine in MCF-7 and MDA-MB-231 cell lines where Noscapine stops the cell cycle during the G2/M phase [76, 77]. A recent study examined the potential use of the drug noscapine (Nos) in combination with docetaxel (DTX) to address treatment resistance in triple negative breast cancer (TNBC) [78]. Tests conducted both in vitro and in vivo on non-small cell lung cancer (NSCLC) showed plausible mechanisms of noscapine based on upregulating caspase-3, Bax, and PARP and downregulating Bcl2 expression, suppressing the growth of xenografted tumors [79]. In another study, the effect of this combination medication of noscapine (Nos) and cisplatin (Cis) on the in vivo mouse xenograft model increased the expression of multiple proteins, including p53, p21, caspase 3, cleaved caspase 3, cleaved PARP, and Bax, and caused the greatest increase in the fraction of apoptotic non-small cell lung cancer (NSCLC) cells [80]. Noscapine increased the radiation susceptibility of GL261 cells, which resulted in a significant delay in tumor growth [81]. Noscapine also inhibited the expression of the proteins for glucose transporter 1, lactate dehydrogenase-B, hexokinase 2, and pyruvate kinase M2, reducing glucose, lactic acid, and ATP levels in HT29/5-FU and LoVo/5-FU cells to prevent the Warburg effect [82]. Recently, Malayer et al. looked into noscapine's cytotoxic and genotoxic effects on cancer cell lines, particularly DU145. The study found that noscapine can dramatically lower prostate cancer cells' viability. DNA damage and a rise in noscapine concentration are associated with this impact [83]. According to a study, noscapine, a therapy for acute lymphoblastic leukaemia, functions better when paired with CYLD, a tumor-growth-inhibiting protein connected to microtubules. CYLD increases noscapine's ability to induce mitotic arrest and apoptosis in ALL cells. Moreover, CYLD increases noscapine's impact on microtubule polymerization, leading to improved microtubule stability and the inhibition of cell division [84].

CONCLUSION

Noscapine, a naturally occurring alkaloid has been used as a cough suppressant since the 1950s due to its antitussive properties. However, certain pharmacological properties of noscapine have been demonstrated by recent cellular study. It has been found that noscapine has antiviral properties by inhibiting the proliferation of numerous viruses, including the human rhinovirus and coronavirus. It has antimalarial properties by inhibiting the expression of the FP-2 protein, which is required for the malaria parasite to survive. Additionally, it has been demonstrated that noscapine induces apoptosis in several cancer cell lines, including those from lung, breast, and prostate cancers. Moreover, noscapine has been shown to decrease microtubule dynamics, which are essential for cell division and proliferation. Noscapine has also been found to block several signalling pathways, including VEGF, EGFR, and NF-

kB. The NF-kB pathway. Noscapine has anticancer properties as well as anti-inflammatory and antioxidant properties. Furthermore, noscapine suppresses brain tumors like glioblastoma by easily passing through the blood-brain barrier. This feature makes it a possible therapy option for brain malignancies. Noscapine is a potentially effective treatment for a range of inflammatory diseases and cancers due to its therapeutic qualities, low systemic toxicity, good oral absorption, and suitable tumor targeting. Furthermore, studies on cells have shown that it can function in conjunction with conventional anticancer drugs, making combination therapy a feasible alternative.

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