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# An *İn vitro* Study on Anticancer Activity of Noscapine

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author FKC designed the study, performed the statistical and biochemical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors II, İB and HA managed the analyses of the study. Author İB managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** Breast cancer is the most common type of cancer among women and ranks second among the causes of female death in the world. In order to find a solution to breast cancer, different studies are being conducted for the treatment and the effects of different drugs and substances on this disease are intensively investigated. Boric acid has been shown to control the proliferation of certain types of cancer cells.Noscapine is one of the ingredients in Papaver somniferum (opium). It was first isolated from Papaver somniferum (opium) in 1817. It is one of the most abundant opioids found in the opium plant (up to 10% of the total composition) after morphine. It is also known as Narcotine, Nectodon, Nospen, Anarcotine, and (archaic) Opiane and occurs in the (-)α isomer which has S, R stereochemistry (S stereochemistry at phthalide-carbon and R at isoquinoline-carbon). Noscapine is structurally and chemically different from other opium alkaloids such as morphine, codeine, thebaine, papaverine, and narceine.
**Materials and Methods:** Based on this information, this study was conducted in vitro to optimize the pure form of noscapine (obtained from the poppy capsule) by applying different concentrations

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on MCF-7 breast cancer cell lines. HPLC technique which is one of the most widely analytical techniques has been used in this study. Determination of the LD50 value and cell proliferation by viability test was also performed to investigate the predicted effects of noscapine on MCF-7 breast cancer cell lines using VEGF (Vascular Endothelial Growth Factor) and PARP (Poly (ADP-Ribose) Polymerase) Analysis.

**Discussion:** According to the results, it was observed in proliferation experiment that the vitality values decreased in direct proportion to the concentration and time at concentrations of 5 ppm, 10 ppm, 25 ppm, 50 ppm, 75 ppm, and 100 ppm. The LD50 value was determined as 50 ppm. There was no significant difference in VEGF values. It was also observed that the PARP level was lower than control group.

**Conclusion:** As a result of the vitality test performed with the CCK-8 kit, it was determined that noscapine has an antiproliferative effect in various concentrations. The low PARP data in the noscapine groups suggests that the cell goes to apoptotic death.

*Keywords: MCF-7, Noscapine, PARP, VEGF.*

## 1. INTRODUCTION

Breast cancer is the most common disease that causes major health problems in women. It is in the first place among all cancer cases seen in women with a rate of 24,1% in our country.[1] Although the incidence and prognosis vary according to geographical regions, it is reported that the incidence of breast cancer increases by 1,5% every year.[2] It is reported in the literature that the most common type of breast cancer has the best survival because it has a 5-year survival rate of 75%. [3-4] MCF-7 cells, a breast cancer cell line, were first isolated in 1970 from the pleural effusion of a 69-year-old woman of invasive ductal carcinoma.[5] This cell line was established by Soule et al. The name MCF-7 is used as the abbreviation of Michigian Cancer Foundation -7. MCF-7, a commonly studied epithelial cancer cell line derived from breast adenocarcinoma, has the characteristics of differentiated breast epithelium [6]. Today the treatments used for cancer are cytotoxic drugs that work somehow by interfering with functions of the cell's DNA. The identification of cytotoxic compounds has led to the development of anti-cancer therapy for years.[7] Noscapine closed molecular formula is C22H23NO7 with molar mass of 413.43 g / mol. Melting point of noscapine is about 176°C. The compound contains 63.91% C, 5.61% H, 3.39% N and 27.09% O atoms. Noscapine, which was previously thought to be narcotic, has been renamed when the antitussive (cough suppressant) property was discovered. It is the same as cough suppressant properties of codeine and because of its antitussive properties; it is used as a medication.[8-11] Noscapine, a cough suppressing agent, was discovered to be an antidrug in phase I / II trials for the treatment of bone marrow cancer. Noscapine does not change the tubulin monomer / polymer ratio.[12-14] Thus, noscapine does not cause circular and neuronal toxicity.[13] This is a feature on anti-microtubule drugs that both over polymerize currently available microtubules and break down polymers into monemers.[15, 16] Extensive studies have reported the potential benefit of noscapine in the treatment of lymphoma, melanoma, prostate, and lung cancer.[17, 18] Noscapine is an alkaloid with little or no effect on organs and blood parameters with low toxicity and also in cancer treatment. It has been reported that as the dose of noscapine increases, hydrogen peroxide production decreases with time. It has also been claimed that noscapine does not accumulate in various tissues. This may be due to the rapid destruction of noscapine in plasma and tissues.[19] The pharmacokinetics studies of noscapine, showing that this drug is rapidly absorbed after oral administration and gives a maximum plasma concentration after 2-3 hours and can be undetectable after 6 hours, and circulates in the system in a short time.[20-23]

## 2. MATERIALS AND METHODS

### 2.1 Sterilization Before Cell Culture

All plastic materials used in cell culture and ready-made sterile media were obtained from commercial companies. Following the incubation, the lysate and medium samples which prepared from the cells were analyzed using the methods described below.

### 2.2 Cell Culture

The main content of the medium used in the culture of MCF-7 human breast adenocarcinoma

cells is RPMI 1640, and it contains 10% fetal bovine serum (FBS) and 1% penicillin / streptomycin. Cell culture was performed by incubating under sterile conditions in a carbon dioxide incubator providing 5% CO2 and 37°C temperature conditions. Sterile prepared medium for cell culture were prepared using T25 and T75 flasks.

Passaging was performed when the cells that have been amplified reached a density of approximately 85% of the culture flask. Cells were used in experiments when they reached a sufficient number.

## 2.3 CCK 8 Cell Viability Test

For the CCK 8 cell viability test (ABP Biosciences AB1714A2), the cells were seeded in a 90-well plate at 90 tal in RPMI medium containing 10% FBS and 1% penicillin / streptomycin at 90 vel and incubated in a 5% CO 2 and 37 ° C incubator. After 24 hours, the wells were divided into 8 groups as shown in Table 1. Three repetitions of each group were performed.

After applications, they were incubated for 48 hours. After 48 hours, 10 CCl of CCK 8 solution was added. Incubation was allowed for 2 hours. At the end of the incubation period, shaking for 10 seconds was applied and measurement at 450 nm wavelength with plate reader was performed.

## 2.4 PARP Analysis

Cells in 75 cm² flask were used for PARP analysis (Sun-Red 201911). Cells were removed with the aid of trypsin. After that, they were centrifuged and the supernatant was discarded and the resulting pellet was turned into suspension with the addition of medium.

24-well cell culture plates were used for the experiment. The MCF-7 human brest adenocarcinoma cell was seeded in wells at a density of $5x10^5$. The plates were allowed to stand in the incubator for 24 hours .Following incubation; the cells were treated with various concentrations of Boron. Then they were placed in a 37ºC incubator for 48 hours. After 48 hours, the cells were removed from the incubator. Media from the plated cells were removed and treated with approximately 700µl of PBS. PBS was withdrawn from the treated cells. 200µl trypsin was added to the cells and placed in a 37ºC incubator and cells were lifted. 450µl of medium was added to the cells separated from the surface to eliminate the effect of trypsin. The cells were transferred to the (eppendorf tube) for PARP by means of a disposable pipette. The cells in the eppendorf tube were centrifuged at 2100 rpm for 15 minutes at 15ºC. After centrifugation, the supernatant was discarded. The medium was added to the eppendorf tube and gently mixed, then added to a 96-well plate loaded with single-use antibody in the kit. Reagents, samples and standards were prepared. Prepared samples and standards were seeded in a 96-well plate and allowed to incubate at 37°C for 60 minutes. After incubation, the wells were washed with wash solution five times each. Chromogen solution A and B were added and incubation at 37°C for 10 minutes was allowed. The stop solution was then added and the measurement was performed.

## 2.5 VEGF Analysis

Cells in 75 cm² flask were used for PARP analysis (Sun-Red 201911). Cells were removed with the aid of trypsin. After that, they were centrifuged and the supernatant was discarded and the resulting pellet was turned into suspension with the addition of medium.

24-well cell culture plates were used for the experiment. The MCF-7 human breast adenocarcinoma cell was seeded in wells at a density of $5x10^5$. The plates were allowed to stand in the incubator for 24 hours .Following incubation; the cells were treated with various concentrations of Boron. They were placed in a 37ºC incubator for 48 hours. After 48 hours, the cells were removed from the incubator. Media from the plated cells were removed and treated with approximately 700µl of PBS. PBS was withdrawn from the treated cells. 200µl trypsin was added to the cells and placed in a 37ºC incubator and cells were lifted. 450µl of medium was added to the cells separated from the surface to eliminate the effect of trypsin. The cells were transferred to the (eppendorf tube) for VEGF analysis with a disposable pipette. The cells in the eppendorf tube were centrifuged at 2100 rpm for 15 minutes at 15ºC. After centrifugation, the supernatant was discarded. The medium was added to the eppendorf tube and gently mixed, then added to a 96-well plate loaded with single-use antibody in the kit. Reagents, samples and standards were prepared. Prepared samples and standards were seeded in a 96-well plate and allowed to incubate at 37°C for 60 minutes. After incubation, the

wells were washed with wash solution five times each. Chromogen solution A and B were added and incubation at 37°C for 10 minutes was allowed. The stop solution was then added and the measurement was performed.

## 2.6 Statistical Analysis

The data were analyzed using SPSS-18 computer program and the results were given as mean ± standard deviation (SD). After the homogeneity of the groups was tested, ANOVA-Duncan test were used in one-way to find differences between groups. Differences were considered statistically significant at $P<0.05$.

After applications, they were allowed to incubate for 48 hours. After 48 hours, 10 µL of CCK 8 solution was added. Incubation was allowed for 2 hours. At the end of the incubation period, they were shaken for 10 seconds and were measured at 450 nm wavelength with plate reader.

## 2.7 Determination of Noscapine Content from Poppy Capsule by HPLC

To determine the amount of Noscapine in this experiment;

Chromatographic analyzes were performed with Agilent brand 12660 HPLC device. UV-Vis detector was used. The device was controlled by ChemStation software.

Column: ACE brand (150 mm x 4.6 mm I. D. 5 µm) was used.

Mobile phase A: water containing 5% acetonitrile

Mobile phase B: Acetonitrile: Acetic acid: Triethylamine (97.9: 2: 0.1, v / v)

Flow rate: 1 ml / min;

Column temperature: 30°C;

Injection volume: 20 µl;

Detection: 284 nm;

Analysis time: 30 minutes.

Extract Preparation: 500 mg of dried ground poppy capsules were weighed and 30 ml of boiled deionized water was added to. The solution was stirred for 15 minutes. Then it was filtered and the pulp was thrown.

Gradient conditions:

Noscapine standard solutions: 1000 ppm Noscapine standard stock solution was prepared and then working standard solutions were prepared at concentrations (100, 200, 300, 400, 500 ppm) by diluting with water from the stock solution.

The poppy capsule was analyzed according to the specified analysis method. It was determined to contain 1.8% noscapine.

## 3. RESULTS

PARP and VEGF analyzes were performed on MCF-7 cell line treated with noscapine at 25 ppm, 50 ppm and 100 ppm concentrations. The results are given in Table 3.

**Table 1. Groups created in the study**

| Groups | Applications made |
|---|---|
| Group 1 | RPMI with 10% FBS and 1% penicillin / streptomycin (Control) |
| Group 2 | 30 µM Cis Platin |
| Group 3 | 5 ppm Noscapine Capsule |
| Group 4 | 10 ppm Noscapine Capsule |
| Group 5 | 25 ppm Noscapine Capsule |
| Group 6 | 50 ppm Noscapine Capsule |
| Group 7 | 75 ppm Noscapine Capsule |
| Group 8 | 100 ppm Noscapine Capsule |

**Table 2. Gradient conditions**

| Time (min) | Mobile phase A (%) | Mobile phase B (%) |
|---|---|---|
| 0 | 90 | 10 |
| 5 | 85 | 15 |
| 10 | 80 | 20 |
| 20 | 65 | 95 |
| 30 | 90 | 10 |

**Table 3. PARP and VEGF results**

| | VEGF | PARP |
|---|---|---|
| Control | 0,10±0,04[a] | 0,11±0,005[a] |
| Noscapine 25 | 0,09±0,02 [a] | 0,05±0,002[b] |
| Noscapine 50 | 0,096±0,07 [a] | 0,07±0,006[a,b] |
| Noscapine 100 | 0,10±0,07 [a] | 0,06±0,006[b] |
| Cis Platin | 0,09±0,08[a] | 0,10±0,003[a] |

***a,b,c: Means in the same column by the same letter are not significantly different according to the one way ANOVA-Duncan test (P<0.05)*

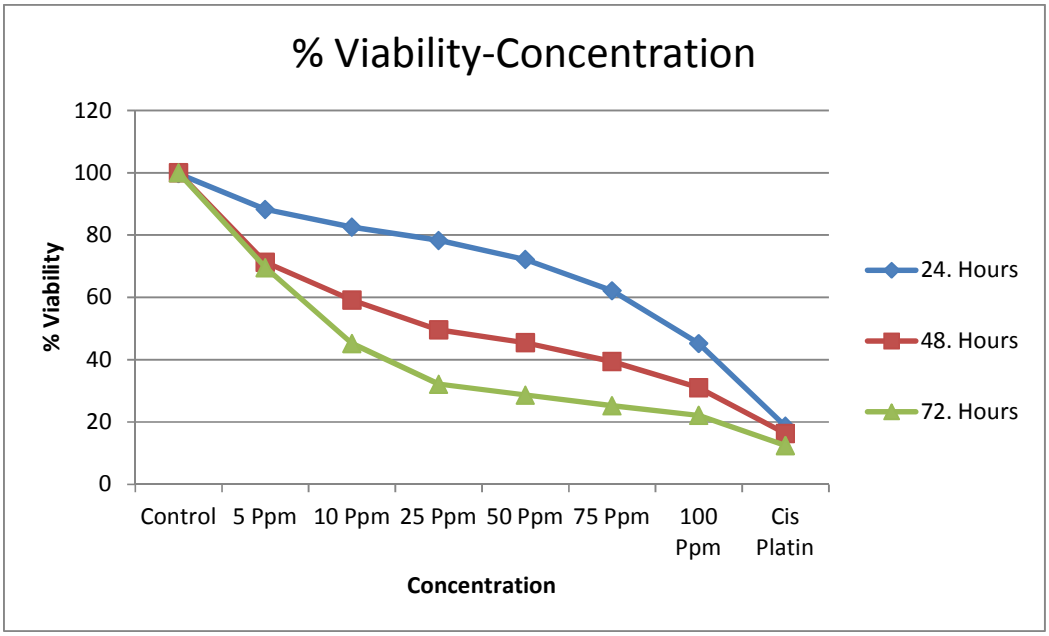


**Fig. 1. Viability-Concentration Graph**

## 4. DISCUSSION

Noskapin is one of the ingredients in Papaver somniferum (opium). It was first isolated from Papaver somniferum (opium) in 1817. It is one of the most abundant opioids found in the opium plant (up to 10% of the total composition) after morphine.

It was used as an antitussive agent, but its anti-neoplastic property was later discovered in 1998.It works as a tubulin inhibitor by connecting stoichiometrically with the tubule, causing a change in its compliance. The development of plant-derived anticancer agents such as noscapine has been highlighted for the last 20 years.

Anticancer activity and synthesis of potent analogues of 9-12 noscapine, a plant-derived anticancer agent, have been reported. Structure-activity analysis has shown that the isoquinoline ring in noscapine (Nos) can be made without affecting the proton binding to tubulin at the C-9 position.[24,25] Due to its antitussive properties, noscapine is often used as an antitussive medication. [9, 11, 26] Based on this information, this study was conducted to investigate the effects of different concentrations of noscapine in MCF-7 breast cancer cell line.

MCF-7, MCF-10F, MDA-MD-231 cell lines were used in the study by Edwin and Gloria on the apoptotic effect of noscapine on breast cancer cell lines. MTT (3- (4,5-dimethylthiazol-2) -2,5-diphenyltetrazolium bromide) method was used to determine the cell viability of these cell lines. The IC-50 value for MCF-10F, MCF-7 and MDA-MB-231 cells at the end of 48 hours was determined as 53,30,20 µM, respectively, with varying doses of noscapine (20-100 µM). It has been shown to induce a concentration-

dependent cytotoxicity in MCF-10F, mcf-7 and MDA-MB-231 cells.[27].

In another study, Mahavir et al. investigated the anticancer activity of Noscapine, an opioid alkaloid, in combination with Cisplatin in human non-small cell lung cancer. Cell viability testing in each treatment group was determined by the crystal violet dye test. Cells were applied with various dilutions of Cis in the presence or absence of Nos at 10-30 and 30-50 µM, respectively, against H460 and A549 cells. Noscapin was found to inhibit proliferation of H460 and A549 cells in a dose-dependent manner with LD50 values of 34.7 ± 2.5 µM and 61.25 ± 5.6 µM, respectively.[28]

In another study; in human colon cancer cells, the SW480 cell line was used and the MTT method was performed to determine cell viability. Six groups (control, noscapine, negative control (NC), siCDH17, NC + noscapine and siCDH17 + noscapine) were used for testing cell viability .The study found that after treatment with 10 µg / mL noscapine, cell proliferation in siCDH17 + noscapine was significantly reduced compared to the noscapine group.[29]. Arezou et al. studied the Synergistic Anticancer Effect of Paclitaxel and Noscapin on Human Prostate Cancer Cell Lines. In this study, the effect of noscapine (10-100) was tested using varying doses to LNCaP and PC-3 prostate cancer cell lines. At the end of 48th hour, the viability of cells was investigated by MTT method. As a result, they showed that single and combination therapies of both paclitaxel and noscapine significantly reduced the viability of both LNCaP and PC-3 cells compared to control cells in a dose and time dependent manner. [30]

In this study, cell viability test was performed using CCK-8 kit to examine the antiproliferative effects of noscapine and to determine the LD50 concentration.

Noscapine was applied to MCF-7 breast cancer cell line at concentrations of 5 ppm, 10 ppm, 25 ppm, 50 ppm, 75 ppm and 100 ppm. Directly a proportional reduction in cell proliferation was observed in the MCF-7 breast cancer cell line at 24, 48, and 72 hours, depending on concentration and time. However, as a result of the very high antiproliferative effect obtained in the 72 hour data, our study was conducted over the 48 hour incubation period, taking other studies as reference. LD50 value was determined as 50 ppm and other analyzes were made over this value.

Poly (ADP-Ribose) Polymerases (PARPs) belong to the family of enzymes that perform multiple cellular processes in addition to DNA repair. PARP1 is best characterized and is one of the PARPs activated by two DNA damage. Poly (ADPRibose) Polymerase (PARP, MA: 116 kDa) is one of the most abundant proteins in the nucleus. It catalyzes the polymerization of ADP-ribose from NAD + molecules in target cellular proteins by attaching to linear or branched polymers. PARP has many roles in most molecules and cellular processes such as DNA damage detection and repair, chromatin modifications, transcription and cellular death pathways. These processes are very critical in physiological and pathological outcomes such as genome repair, carcinogenesis, aging, inflammation, and neuron function.[31] PARP which is one of the first identified substrates of caspase has vital role especially in apoptosis and necrosis. In the apoptosis process, caspase 7 and caspase 3 cleave PARP between Asp214 and Gly215 and break down p85 and p25. The PARP cleavage separates DBD from the catalytic domain and inactivates the enzymes. This eliminates PARP activation in response to DNA fragmentation during apoptosis and hinders the necessary ATP consumption in necrotic cell death and the futile efforts required for DNA repair. Thus, PARP cleavage helps the cell enters the apoptotic pathway and is recognized as the distinctive feature of apoptosis.[31,32] PARP works according to the amount of damage in DNA. If DNA damage is very high, PARP leads the cell to necrosis with ATP / NAD consumption. If DNA damage is minimal, PARP, along with other DNA repair enzymes, can help the cell survive. Caspase, which plays a critical role in apoptosis and is the main responsible for the cleavage of PARP, when activated, the cell goes into apoptosis by performing PARP cleavage.[33]In this study, it was observed that PARP values decreased significantly compared to the control group and Cis Platin group. These results suggest that the applied noscapine concentrations lead to apoptotic death of cells. Although there is no significant difference between the Noscapine groups, the most effective concentration is 25 ppm.

Cancer cells secrete a number of angiogenic factors (VEGF, epidermal growth factor (EGF), and interleukin-18). Many of these factors act on different small vessels and their binding to the receptors in the endothelial cell, resulting in new vessels.[34, 35] The effects of Noscapine on VEGF were also examined, but no significant

difference was found between the control and Cis Platin groups and the noscapine groups.

## 5. CONCLUSION

As a result of the vitality test performed with the CCK-8 kit, it was determined that noscapine has an antiproliferative effect in various concentrations. PARP analysis has been done. As a result of the analysis, PARP levels were lower than the control group. This result suggests that the cells perform apoptotic death.

## ETHİCAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

## COMPETİNG İNTERESTS

Authors have declared that no competing interests exist.

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