Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2026;7(2):79–82

YORUM / COMMENTARY

Acetaminophen and Its Potential Anticancer Effects in Non-Small Cell Lung Cancer via Serotonin-Mediated Cellular Mechanisms

Küçük Hücreli Dışı Akciğer Kanserinde Asetaminofen'in Serotonin Aracılı Hücresel Mekanizmalar Yoluyla Potansiyel Antikanser Etkileri

Ayşegül Akbay, Rabia Şeyma Nur Taşdemir*

Yuksek Ihtisas University, Faculty of Medicine, Department of Medical Biochemistry, Ankara, Türkiye
Yüksek İhtisas Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya Anabilim Dalı, Ankara, Türkiye

ABSTRACT

This commentary article explores the hypothesis that acetaminophen may exert an anticancer effect in Non- small cell lung cancer cells through serotonin-related mechanisms, discussing potential molecular interactions, signaling pathways, and therapeutic implications.

Keywords: Cancer, non- small cell lung cancer, acetaminophen, serotonin

ÖZ

Bu yorum makalesinde, asetaminofen'in serotonin ile ilişkili mekanizmalar yoluyla küçük hücreli dışı akciğer kanseri hücrelerinde antikanser etki gösterebileceği hipotezi araştırılmakta, olası moleküler etkileşimler, sinyal yolları ve terapötik etkiler tartışılmaktadır.

Anahtar Sözcükler: Kanser, küçük hücreli dışı akciğer kanseri, asetaminofen, serotonin

Introduction

Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality worldwide, accounting for approximately 85% of all lung cancer cases (1). Despite advances in targeted therapies and immunotherapies, many patients still experience poor prognoses due to resistance and relapse. As a result, there is an ongoing search for novel treatment strategies that can complement or enhance existing therapeutic approaches.

One such potential candidate is acetaminophen (paracetamol), a widely used analgesic and antipyretic drug. Although acetaminophen is not traditionally classified as an anticancer agent, recent research has suggested that it may exert cytotoxic effects on cancer cells, including NSCLC (2). Among the proposed mechanisms of its anticancer activity, one intriguing possibility is its potential interaction with serotonin-mediated cellular pathways, which are increasingly recognized as playing a role in cancer progression (3).

Since we are interested in the relationship between NSCLC cells and neuromodulation, we wanted to dig into this topic. Therefore, this commentary article explores the hypothesis that acetaminophen may influence anticancer processes in NSCLC cells through serotonin-related mechanisms, discussing possible molecular interactions, signaling pathways, and therapeutic implications.

Serotonin and Cancer: A Growing Area of Interest

Serotonin (5-hydroxytryptamine, 5-HT) is a well-known neurotransmitter that regulates mood, cognition, and various physiological functions. However, emerging evidence indicates that serotonin also affects cancer biology through its influence on cell proliferation, apoptosis, angiogenesis, and immune modulation (4).

Serotonin acts primarily through 5-HT receptors (5-HTRs), which are expressed in various tissues, including the lungs.

Cite this article as: Akbay A, Nur Taşdemir RŞ. Acetaminophen and Its Potential Anticancer Effects in NSCLC via Serotonin-Mediated Cellular Mechanisms. YIU Saglik Bil Derg 2026;7(2):79–82. https://doi.org/10.51261/yiu.2026.1665391

***Yazışma Adresi/ Correspondence Address:** Rabia Şeyma Nur Taşdemir, Yüksek İhtisas Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya Anabilim Dalı, Ankara, Türkiye
E-posta: rabiaseymanurtasdemir@yiu.edu.tr; A.A.: 0009-0003-6793-4887; R.Ş.N.T.: 0000-0003-1364-3614

Geliş Tarihi/Received: 07.04.2025, **Kabul Tarihi/Accepted:** 15.12.2025, **Çevrimiçi Yayın Tarihi/ Available Online Date:** 27.08.2026

Creative Commons Atıf-Ticari Olmayan 4.0 Uluslararası Lisansı altında lisanslanmıştır.

Several 5-HT receptor subtypes have been implicated in tumorigenesis, particularly 5-HT1 and 5-HT2 receptors, which may influence cancer cell survival, migration, and invasion (5). The involvement of serotonin in NSCLC suggests that pharmacological modulation of serotonin signaling could represent a novel therapeutic approach.

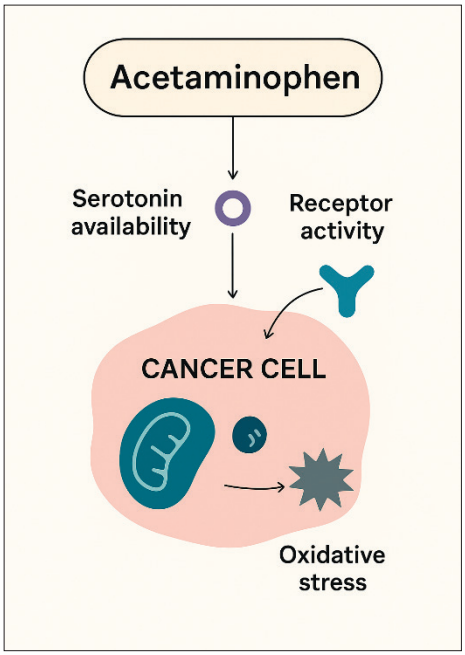
Serotonin-Mediated Pathways in NSCLC

In NSCLC, serotonin signaling has been linked to:

- Proliferation and Survival: Activation of 5-HT receptors, particularly 5-HT2A and 5-HT2B, appears to stimulate mitogenic pathways such as Ras-MAPK and PI3K-Akt, thereby promoting cell survival and proliferation (4, 5).
- Angiogenesis: Serotonin may contribute to tumor vascularization by enhancing endothelial cell migration and VEGF expression (5).
- Evasion of Apoptosis: Serotonin-mediated activation of anti-apoptotic proteins (e.g., Bcl-2, survivin) could help support NSCLC cell survival, making this pathway a potential target for intervention (6).

Given this background, the possibility that acetaminophen modulates serotonin-related processes in NSCLC presents an intriguing avenue for exploration.

Acetaminophen's Mechanisms of Action and Its Potential Link to Serotonin Signaling



Acetaminophen's conventional mechanisms include inhibition of cyclooxygenase (COX) enzymes, reduction of prostaglandin synthesis, and modulation of oxidative stress. However, recent studies suggest that acetaminophen may also influence serotonin-related pathways in cancer cells (2). While direct evidence in NSCLC is currently limited, the following mechanisms offer a theoretical basis for further investigation.

1. Acetaminophen and Serotonin Availability

Acetaminophen is known to increase central serotonin levels by promoting the production of serotonin derivatives such as AM404 (N-arachidonoylphenolamine) (7). AM404 acts on transient receptor potential vanilloid 1 (TRPV1) channels and cannabinoid receptor CB1, both of which have been linked to apoptotic pathways in cancer cells (8).

However, a critical distinction must be made regarding the location of this metabolism. While the conversion of acetaminophen to AM404 is a documented phenomenon in the central nervous system (CNS) contributing to its analgesic effects (7), it is crucial to note that this metabolic conversion has not yet been demonstrated in solid tumor models or NSCLC specifically.

Nevertheless, if future research confirms that NSCLC cells or the surrounding tumor microenvironment possess the enzymatic capacity to metabolize acetaminophen into AM404, this pathway could represent a novel mechanism of action. In this hypothetical scenario, acetaminophen-induced AM404 formation could:

- Potentially interfere with serotonin-induced tumorigenic signaling by competing with serotonin at receptor sites.
- Promote apoptosis via CB1 activation, leading to downstream modulation of pro-apoptotic factors such as Bax and caspases.

2. Acetaminophen as a 5-HT Receptor Modulator

Evidence suggests that acetaminophen may exert indirect effects on serotonin receptor activity, though the translation of these effects to the oncology setting remains speculative. Specifically:

- It has been shown to reduce serotonin turnover (9), if a similar reduction occurs in the lung tumor microenvironment, it could potentially diminish the activation of pro-survival 5-HT receptors in NSCLC.
- Acetaminophen may theoretically downregulate 5-HT2 receptor expression, which is commonly overexpressed in lung cancer and associated with tumor growth (10).
- By altering serotonin receptor signaling, acetaminophen could shift the balance toward apoptotic rather than proliferative pathways, thereby potentially offering an anticancer benefit.

3. Acetaminophen-Induced Oxidative Stress and Its Impact on Serotonin Signaling

Acetaminophen is known to induce oxidative stress at high doses, leading to mitochondrial dysfunction and apoptosis. Interestingly, serotonin-mediated signaling also interacts with oxidative stress pathways. In NSCLC:

- Excess serotonin can protect cancer cells from oxidative damage by upregulating antioxidant enzymes (e.g., superoxide dismutase, glutathione peroxidase).

- Acetaminophen-induced oxidative stress could potentially override serotonin's protective effects, leading to increased susceptibility of NSCLC cells to apoptosis.

This suggests a possible synergistic mechanism where acetaminophen may counteract serotonin-driven resistance to oxidative stress, thereby facilitating cancer cell death.

Drugs That Influence Serotonin Signaling and Their Potential Impact on Cancer Pathophysiology

Beyond acetaminophen, several commonly used drug classes that modulate serotonin signaling — such as antiemetics and selective serotonin reuptake inhibitors (SSRIs) — may also influence cancer biology.

1. Antiemetics (5-HT$_3$ Receptor Antagonists)

Drugs like ondansetron and granisetron, which act as 5-HT$_3$ receptor antagonists, are routinely used to control chemotherapy-induced nausea and vomiting (11). Emerging evidence suggests that these agents could exert additional effects on tumor biology (12). Preclinical studies indicate that 5-HT$_3$ blockade may reduce proliferation and induce apoptosis in certain cancer cell types, possibly by interfering with serotonin-driven growth signals and modulating autophagic pathways (11, 13).

In retrospective clinical analyses, perioperative or adjuvant use of 5-HT$_3$ receptor antagonists has been associated with improved outcomes in lung cancer (11), though causality remains unproven. These findings raise the possibility that serotonin receptor blockade might influence tumor microenvironmental dynamics or immune cell signaling in ways that complement standard oncologic therapies.

2. Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs such as fluoxetine and sertraline, widely prescribed for depression, affect serotonin availability by inhibiting its reuptake. Laboratory studies have reported that SSRIs can induce apoptosis or reduce viability in various cancer cell lines, potentially through mitochondrial pathways or direct interactions with serotonin receptors (14, 15).

However, the net impact of SSRIs on cancer progression appears to vary depending on tumor type, serotonin receptor expression, and dose. Some studies suggest anti-proliferative or pro-apoptotic effects, whereas others indicate potential tumor-supportive roles under specific conditions (16). These mixed outcomes underscore the complexity of serotonin's role in cancer pathophysiology and highlight the need for carefully controlled investigations into how serotonin-modulating drugs interact with oncogenic pathways.

3. Implications for NSCLC

Given that serotonin signaling contributes to NSCLC cell proliferation, angiogenesis, and immune evasion, drugs that alter serotonin levels or receptor activity could potentially influence tumor behavior. While current evidence is largely indirect, integrating findings from acetaminophen, SSRIs, and antiemetics suggests that modulation of serotonin pathways may represent a broader therapeutic opportunity in NSCLC. Controlled experimental studies are needed to determine whether these effects are clinically meaningful and mechanistically linked.

Preclinical Evidence Supporting Acetaminophen's Potential Anticancer Activity in NSCLC

Several studies have reported possible anticancer effects of acetaminophen in lung cancer models:

- In vitro studies have shown that acetaminophen in combination with other agents may reduce NSCLC cell viability, possibly through mitochondrial damage and apoptosis induction (17).
- Serotonin-targeting studies in NSCLC have found that pharmacological inhibition of serotonin receptors can reduce tumor growth (18), supporting the idea that acetaminophen's interaction with serotonin pathways might be beneficial.

While these findings are promising, further research is needed to establish a direct causal link between acetaminophen's effects on serotonin and its potential anticancer properties.

Therapeutic Implications and Future Directions

If acetaminophen's anticancer effects in NSCLC are confirmed to be mediated through serotonin-related mechanisms, several important therapeutic implications could emerge:

- *Repurposing Acetaminophen as an Adjunct to NSCLC Therapy*

Acetaminophen might be used in combination with existing therapies (e.g., tyrosine kinase inhibitors, immune checkpoint inhibitors) to enhance treatment efficacy. Given its low cost and widespread availability, acetaminophen could offer an accessible option for resource-limited settings.

- *Targeting Serotonin Signaling in NSCLC*

If acetaminophen's anticancer effects are linked to serotonin modulation, selective 5-HT receptor antagonists could be investigated as complementary treatments. Combination therapies involving acetaminophen and serotonin-targeting drugs may warrant exploration to maximize therapeutic benefits.

- *Potential Biomarkers for Patient Selection*

Identifying serotonin receptor expression profiles in NSCLC patients could help determine which individuals are most likely to respond to acetaminophen-based therapies. Measuring serotonin metabolites in plasma or tumor tissues might serve as a biomarker for treatment response.

Conclusion

While traditionally considered an analgesic, acetaminophen has been suggested to have potential anticancer effects in preclinical models. The hypothesis that acetaminophen may influence NSCLC progression via serotonin-mediated mechanisms is entirely theoretical and has not yet been demonstrated experimentally.

Although the modulation of serotonin availability and receptor activity by acetaminophen is well-documented in other physiological contexts, its occurrence in NSCLC remains to be proven. Specifically, the conversion of acetaminophen to AM404, while established in the CNS, represents a novel hypothetical target in the lung tumor microenvironment. Despite the lack of direct evidence, acetaminophen's established safety profile makes it an attractive candidate for further study. As research into serotonin's role in cancer expands, exploring acetaminophen — alongside other serotonin-modulating agents — in NSCLC treatment strategies could provide a novel, cost-effective avenue for future therapeutic development.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: None

Author Contributions: Concept - AA, RŞNT; Design - AA, RŞNT; Supervision - AA, RŞNT; Literature Search - RŞNT; Analysis or Interpretation - AA, RŞNT; Writing - AA; Critical Review - AA, RŞNT

References

1. Sorin M, Prosty C, Ghaleb L, Nie K, Katergi K, Shahzad MH, Dubé LR, Atallah A, Swaby A, Dankner M, Crump T, Walsh LA, Fiset PO, Sepesi B, Forde PM, Cascone T, Provencio M, Spicer JD. Neoadjuvant Chemoimmunotherapy for NSCLC: A Systematic Review and Meta-Analysis. JAMA Oncol 2024;10(5):621–633. https://doi.org/10.1001/jamaoncol.2024.0057
2. Wu J, Maller B, Kaul R, Galabow A, Bryan A, Neuwelt A. High-Dose Acetaminophen as a Treatment for Cancer. Livers 2024;4:84–93. https://doi.org/10.3390/livers4010007
3. Irinmwinuwa NEO, Unekwe NPC, Egba NEU, Metu NEC, Cherech NNC. Acetaminophen: Ancient drug with a novel analgesic mechanism of action. WJARR 2022;16(1):580–589. https://doi.org/10.30574/wjarr.2022.16.1.1046
4. Chen L, Huang S, Wu X, He W, Song M. Serotonin signalling in cancer: Emerging mechanisms and therapeutic opportunities. Clin Transl Med. 2024 Jul;14(7):e1750. https://doi.org/10.1002/ctm2.1750
5. Mao L, Xin F, Ren J, Xu S, Huang H, Zha X, Wen X, Gu G, Yang G, Cheng Y, Zhang C, Wang W, Liu X. 5-HT2B-mediated serotonin activation in enterocytes suppresses colitis-associated cancer initiation and promotes cancer progression. Theranostics 2022;12(8):3928–3945. https://doi.org/10.7150/thno.70762
6. Karmakar S, Lal G. Role of serotonin receptor signaling in cancer cells and anti-tumor immunity. Theranostics 2021;11(11):5296–5312. https://doi.org/10.7150/thno.55986
7. Al-kuraishy HM, Al-Gareeb A, Albuhadily A, Abdelmaksoud E, Alexiou A, Papadakis M, Batiha G. The efficacy and safety of Acetaminophen for pain relief. Authorea. 2024. https://doi.org/10.22541/au.171361353.33776062/v1
8. Bunsick DA, Matsukubo J, Aldbai R, Baghaie L, Szewczuk MR. Functional Selectivity of Cannabinoid Type 1 G Protein-Coupled Receptor Agonists in Transactivating Glycosylated Receptors on Cancer Cells to Induce Epithelial–Mesenchymal Transition Metastatic Phenotype. Cells 2024;13(6):480. https://doi.org/10.3390/cells13060480
9. Pickering G, Loriot MA, Libert F, Eschalier A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clinical Pharmacology & Therapeutics 2006;79(4):371-378.
10. Hamurtekin Y, Nouilati A, Demirbatir C, Hamurtekin E. The Contribution of Serotonergic Receptors and Nitric Oxide Systems in the Analgesic Effect of Acetaminophen: An Overview of the Last Decade. Turk J Pharm Sci 2020;17(1):119-126. https://doi.org/10.4274/tjps.galenos.2018.35403
11. Lee JS, Park SY, Kim NY, Kim DW, Oh JE, Heo E, Lee JS, Yoo YC. Anti-Tumor Potential of a 5-HT3 Receptor Antagonist as a Novel Autophagy Inducer in Lung Cancer: A Retrospective Clinical Study with In Vitro Confirmation. J Clin Med. 2019 Sep 3;8(9):1380. https://doi.org/10.3390/jcm8091380.
12. Yoo YC, Lin L, Lee S, Shin YR, Oh JE, Kim NY. Palonosetron, a 5-HT3 Receptor Antagonist, Induces G1 Cell Cycle Arrest and Autophagy in Gastric Cancer Cells. Int J Mol Sci. 2025 Oct 15;26(20):10039. https://doi.org/10.3390/ijms262010039.
13. Ataee R, Ajdary S, Rezayat M, Shokrgozar MA, Shahriari S, Zarrindast MR. Study of 5HT3 and HT4 receptor expression in HT29 cell line and human colon adenocarcinoma tissues. Arch Iran Med. 2010 Mar;13(2):120-5.
14. Serafeim A, Holder MJ, Grafton G, Chamba A, Drayson MT, Luong QT, Bunce CM, Gregory CD, Barnes NM, Gordon J. Selective serotonin reuptake inhibitors directly signal for apoptosis in biopsy-like Burkitt lymphoma cells. Blood. 2003 Apr 15;101(8):3212-9. https://doi.org/10.1182/blood-2002-07-2044.
15. Duarte D, Vale N. Antidepressant Drug Sertraline against Human Cancer Cells. Biomolecules. 2022 Oct 19;12(10):1513. https://doi.org/10.3390/biom12101513. PMID: 36291722; PMCID: PMC9599050.
16. Ballou Y, Rivas A, Belmont A, Patel L, Amaya CN, Lipson S, Khayou T, Dickerson EB, Nahleh Z, Bryan BA. 5-HT serotonin receptors modulate mitogenic signaling and impact tumor cell viability. Mol Clin Oncol. 2018 Sep;9(3):243-254. https://doi.org/10.3892/mco.2018.1681.
17. Gai C, Yu M, Li Z, Wang Y, Ding D, Zheng J, Lv S, Zhang W, Li W. Acetaminophen sensitizing erastin-induced ferroptosis via modulation of Nrf2/heme oxygenase-1 signaling pathway in non-small-cell lung cancer. J Cell Physiol. 2020 Apr;235(4):3329-3339. https://doi.org/10.1002/jcp.29221. Epub 2019 Sep 20. PMID: 31541463.
18. Du X, Wang T, Wang Z, Wu X, Gu Y, Huang Q, Wang J, Xie J. 5-HT7 Receptor Contributes to Proliferation, Migration and Invasion in NSCLC Cells. Onco Targets Ther. 2020 Mar 9;13:2139-2151. https://doi.org/10.2147/OTT.S244339.