

# Bax/Bcl-2 Ratio as the Golden Marker of Apoptosis: Molecular Mechanisms and Regulatory Pathways

Ghea Farmaning Thias Putri<sup>1</sup> and Zahara Nurfatihah Z<sup>2\*</sup>

\*Correspondence:

[zaharanurfatihahz@fk.unila.ac.id](mailto:zaharanurfatihahz@fk.unila.ac.id)

<sup>1</sup> Department of Medical Biology, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia

<sup>2</sup> Department Biochemistry, Molecular Biology and Physiology, Faculty of Medicine, Universitas Lampung, Bandar Lampung 35145, Indonesia

Submission October 02, 2025

Accepted October 11, 2025

Available online on October 13, 2025

©2025 The Authors. Published by Stem Cell and Cancer Research, Semarang, Indonesia. This is an open-access article under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike License ([CC BY-NC-SA 4.0](https://creativecommons.org/licenses/by-nc-sa/4.0/)), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## ABSTRACT

Apoptosis is an essential biological mechanism responsible for maintaining tissue homeostasis by removing unnecessary or damaged cells. Among the key molecular regulators, the interplay between the pro-apoptotic protein Bax and the anti-apoptotic protein Bcl-2 determines cellular fate. The Bax/Bcl-2 ratio has been recognized as the “golden marker” of apoptosis, representing the fine equilibrium between survival and death signaling pathways within cells. This review aims to provide an updated overview of recent advances in understanding the molecular mechanisms and regulatory networks that control the Bax/Bcl-2 ratio and its significance as a diagnostic and therapeutic biomarker. Relevant studies were systematically identified from PubMed, Scopus, ScienceDirect, and Google Scholar, focusing on publications from 2020 to 2025. Current evidence suggests that the Bax/Bcl-2 ratio is influenced by transcriptional regulation involving p53, NF-κB, and Akt/PI3K pathways, as well as by post-translational modifications such as phosphorylation and ubiquitination that govern mitochondrial membrane permeabilization. Clinically, alterations in this ratio correlate with disease progression, therapeutic response, and prognosis in cancer, neurodegenerative, and renal disorders. Targeting this ratio through modulation of upstream regulators or BH3 mimetics offers promising therapeutic potential. In conclusion, a deeper understanding of the Bax/Bcl-2 ratio provides crucial perspectives for advancing diagnostic innovation and developing targeted therapies for apoptosis-related diseases.

**Keywords:** Bax/Bcl-2 ratio, Apoptosis, Molecular mechanisms, Diagnostic and therapeutic biomarker.

## INTRODUCTION

Apoptosis is an essential process of programmed cell death that controls cell numbers and maintains tissue homeostasis in multicellular organisms. It functions as a natural counterpart to mitosis and is essential for normal development as well as for the preservation of physiological balance<sup>1</sup>. Dysregulation of this process is strongly associated with a wide range of pathological conditions. Insufficient apoptosis allows abnormal cells to survive, thereby promoting tumor formation<sup>2</sup>, while excessive apoptosis contributes to the progression of acute and chronic degenerative disorders such as ischemic stroke, Alzheimer’s disease, Parkinson’s disease, and degenerative bone conditions<sup>3</sup>. A detailed understanding of the molecular mechanisms that regulate apoptosis is therefore fundamental for elucidating disease pathogenesis and for developing effective targeted therapeutic strategies<sup>4</sup>.

Apoptosis proceeds through two main signaling pathways known as the extrinsic and intrinsic pathways, which work together to determine the fate of a cell. The extrinsic apoptotic pathway is initiated by extracellular stimuli in which death ligands interact with their specific receptors located on the plasma membrane. This binding event promotes the assembly of the death-inducing signaling complex (DISC) and subsequently triggers the activation of caspase-8, which initiates a downstream cascade of apoptotic reactions. In contrast, the intrinsic or mitochondrial apoptotic pathway is controlled by the B-cell lymphoma 2 (Bcl-2) family of proteins that controls mitochondrial outer membrane permeability and cytochrome c release. These events subsequently activate initiator caspases that execute cell death<sup>5</sup>. Among the two pathways, the mitochondrial pathway represents the central and predominant mechanism of apoptosis, as it integrates various intracellular stressors such as DNA damage, oxidative imbalance, metabolic disruption, and endoplasmic reticulum stress, all of which converge on mitochondrial outer membrane permeabilization, an irreversible step leading to cell death<sup>6</sup>.

The Bcl-2 protein family serves as a key modulator in regulating the interplay between apoptosis-promoting and apoptosis-inhibiting signals. Pro-apoptotic members such as Bax and Bak facilitate cell death by assembling into oligomeric complexes within the mitochondrial outer membrane, enabling the translocation of cytochrome c into the cytosol and subsequently triggering the activation of caspase enzymes. Conversely, anti-apoptotic counterparts including Bcl-2 and Bcl-XL counteract this process by blocking Bax and Bak oligomerization and safeguarding mitochondrial membrane stability<sup>7</sup>. The dynamic balance between these opposing protein factions is critical for sustaining cellular equilibrium, and any disruption in this homeostatic mechanism can determine whether a cell undergoes survival or programmed death<sup>8</sup>.

The Bax/Bcl-2 ratio has emerged as the “golden marker” of apoptosis because it provides a reliable indicator of the equilibrium between apoptosis-promoting and apoptosis-inhibiting signals. A high Bax/Bcl-2 ratio indicates a tendency toward the activation of pro-apoptotic pathways and an increased population of apoptotic cells, whereas a low ratio indicates enhanced cell survival and resistance to apoptosis,<sup>7-9</sup> further confirmed that a significant elevation of the Bax/Bcl-2 ratio activates the apoptotic signaling cascade, as evidenced by elevated caspase-3 activity. Numerous experimental and clinical studies have also demonstrated that alterations in this ratio correlate strongly with disease progression and therapeutic response. For instance, low Bax/Bcl-2 ratios have been associated with poor chemotherapy response and unfavorable prognosis in patients with acute myeloid leukemia<sup>10,11</sup>. Similarly, an increased ratio was found to predict better remission outcomes in pediatric acute lymphoblastic leukemia<sup>12</sup>, while dysregulation of Bax and Bcl-2 expression contributed to bortezomib resistance in mantle cell lymphoma<sup>13</sup>. Thus, the Bax/Bcl-2 ratio represents not only a molecular hallmark of apoptosis but also a potential prognostic and therapeutic biomarker.

Despite significant advances in understanding apoptotic signaling, the precise molecular mechanisms and regulatory networks governing the Bax/Bcl-2 ratio recognized as the golden marker of apoptosis remain incompletely defined. This ratio is modulated by multi-layered control mechanisms including transcriptional regulation, post-translational modifications, and upstream signaling cascades that collectively determine mitochondrial integrity and cell fate. Therefore, this review presents an integrated overview of recent findings on the molecular mechanisms and regulatory pathways underlying the Bax/Bcl-2 ratio, emphasizing its pivotal role as both a hallmark of apoptosis and a promising diagnostic and therapeutic target in apoptosis-related diseases.

## MATERIALS AND METHODS

### *Literature Search Strategy*

This review was conducted through a systematic search and analysis of relevant literature obtained from four major databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. The keywords used included “Bax/Bcl-2 ratio”, “apoptosis marker”, “molecular mechanism of apoptosis”, “Bax”, and “Bcl-2”. Only peer-reviewed original research and review articles published in English were considered. Duplicates and non-scientific sources, such as conference abstracts and preprints, were excluded. The search encompassed studies published between 2020 and 2025, with emphasis on recent advancements over the past decade.

### *Inclusion and Exclusion Criteria*

This review was conducted through a systematic search and analysis of relevant literature obtained from four major databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. Articles were included if they (1) investigated Bax and Bcl-2 expression or their ratio in the context of apoptosis, (2) reported quantitative or qualitative data on apoptotic markers, and (3) examined correlations with disease progression or therapeutic response. Studies were excluded if they lacked molecular analysis, were case reports without experimental data, or focused on unrelated apoptotic pathways without addressing Bax/Bcl-2 regulation.

### *Data Extraction and Analysis*

Data from eligible studies were independently reviewed and extracted by the authors. Information regarding experimental design, cellular models, disease type, Bax and Bcl-2 expression levels, apoptosis assays, and key findings were summarized. The extracted data were synthesized qualitatively to identify consistent patterns, molecular pathways, and potential gaps in current knowledge. Cross-study comparisons were performed to highlight the relevance of the Bax/Bcl-2 ratio as a diagnostic, prognostic, and therapeutic biomarker.

## RESULTS

### *The Role of the Bax/Bcl-2 Ratio in Determining Cell Fate*

Programmed cell death, or apoptosis, relies heavily on the equilibrium between pro-apoptotic and anti-apoptotic members of the Bcl-2 family. The pro-apoptotic protein Bax becomes activated and relocates to the mitochondrial membrane, where it oligomerizes to trigger cytochrome c release into the cytosol, consequently activating the caspase cascade that drives apoptosis. In contrast, Bcl-2 acts as a cell survival regulator by binding to Bax or BH3-only proteins, thereby blocking Bax oligomerization and maintaining mitochondrial membrane integrity. Hence, the balance between Bax and Bcl-2 expression, represented by the Bax/Bcl-2 ratio, serves as a crucial determinant of cell fate—where a higher ratio favors apoptotic signaling, while a lower ratio supports cell survival<sup>14-16</sup>.

Both *in vitro* and *in vivo* studies support the importance of this ratio as a determinant of apoptosis. In pancreatic cancer cell models, an elevated Bax/Bcl-2 ratio induced by oxidative stress has been shown to enhance caspase-3 activation and apoptosis, while cells with a lower ratio-maintained viability despite DNA damage. Similarly, studies in neuronal and renal cells demonstrated that a high Bax/Bcl-2 ratio correlates with increased sensitivity to oxidative stress or genetic injury<sup>17,18</sup>.

### ***Transcriptional and Translational Regulation of Bax and Bcl-2 Expression***

Bax and Bcl-2 protein expression is regulated by various transcription factors that respond to cellular stress. The transcription factor p53 is a major regulator that activates Bax transcription in response to DNA damage, driving the cell toward apoptosis<sup>19</sup>. In contrast, the Akt/PI3K and NF- $\kappa$ B pathways stimulate Bcl-2 expression, providing cytoprotective effects by suppressing caspase<sup>20,21</sup>. Additionally, BH3-only proteins, including Bad, Bim, and Puma, function as key modulators of the Bax/Bcl-2 ratio through competitive binding mechanisms. By associating with Bcl-2, these proteins release Bax from inhibitory complexes, promoting its oligomerization and subsequent activation of apoptosis. This highlights the precise coordination between pro- and anti-apoptotic signaling through both transcriptional and translational mechanisms<sup>22-24</sup>.

### ***Post-Translational Modifications and Functional Activity***

Beyond transcriptional regulation, Bax and Bcl-2 activities are also controlled by post-translational modifications (PTMs). Phosphorylation, ubiquitination, acetylation, and proteasomal degradation alter the stability and interactions of these proteins, thereby influencing mitochondrial membrane permeability<sup>25</sup>. Bcl-2 phosphorylation at serine-70 increases its ability to inhibit apoptosis by reinforcing its binding to Bax and preserving mitochondrial membrane integrity. Conversely, Bax ubiquitination reduces its stability and pro-apoptotic activity, thereby suppressing apoptosis<sup>24,26</sup>. The complex interplay between transcriptional regulation and post-translational modifications thus establishes a finely tuned system to maintain an optimal Bax/Bcl-2 ratio and ensure proper control of cell fate<sup>26</sup>.

### ***Mitochondrial Outer Membrane Permeabilization (MOMP) and Apoptotic Pathway Activation***

Elevation of the Bax relative to Bcl-2 serves as a critical step for inducing MOMP (Kuwana et al., 2020). Bax oligomers form channels within the mitochondrial membrane, allowing cytochrome c and additional apoptogenic proteins, including Smac/DIABLO, to be released into the cytoplasm. Once released, cytochrome c binds to Apaf-1 and procaspase-9, triggering apoptosome formation and subsequent caspase-3 activation, which executes apoptosis<sup>21</sup>. Meanwhile, Bcl-2 acts as a mitochondrial guardian by neutralizing Bax, thereby preventing pore formation and cytochrome c release. The imbalance between these two proteins thus functions as a key regulator of whether the cell persists or undergoes apoptosis<sup>14,19</sup>.

### ***Clinical Relevance and Therapeutic Strategies***

Alterations in Bax and Bcl-2 expression and their regulatory mechanisms have significant implications for therapeutic responses. Cancer cells with a low Bax/Bcl-2 ratio tend to exhibit resistance to chemotherapy and radiotherapy, whereas increasing this ratio enhances sensitivity to apoptosis-inducing agents<sup>22,27</sup>. Modern therapeutic strategies aim to target these regulatory pathways—either by suppressing Bcl-2 expression using specific inhibitors such as venetoclax, or by upregulating Bax through p53 activation or BH3 mimetics. A deeper understanding of the transcriptional and post-translational regulation of Bax and Bcl-2 opens new opportunities for developing more effective therapies to overcome apoptosis resistance<sup>27</sup>.

## DISCUSSION

### *Bax-to-Bcl-2 Ratio as a Principal Regulator of Cellular Apoptosis*

Programmed cell elimination is a precisely controlled mechanism influenced by the relative levels of death-promoting and survival-promoting Bcl-2 family proteins. The Bax-to-Bcl-2 ratio integrates the functional activities of these proteins, offering a more informative measure than examining each protein individually. Upon activation, Bax forms oligomers in the mitochondrial outer membrane, triggering mitochondrial permeabilization, cytochrome c release, and caspase cascade activation, whereas Bcl-2 opposes these effects by maintaining mitochondrial integrity<sup>13,26</sup>. Therefore, the Bax-to-Bcl-2 ratio establishes the apoptotic threshold and serves as a principal regulator of cellular destiny.

### *The Bax/Bcl-2 Ratio as a “Golden Marker” of Apoptosis*

The Bax-to-Bcl-2 ratio has been consistently identified as a molecular indicator of the life–death decision, representing the equilibrium of death-promoting and survival-promoting cues across multiple biological contexts. This role is preserved across diverse tissues and cell models, including cancer cells, neurons, and renal tissue, establishing the Bax-to-Bcl-2 ratio as a universal regulator of programmed cell elimination. In various cancers, an elevated Bax/Bcl-2 ratio correlates with favorable clinical outcomes and enhanced therapeutic response. Studies involving patients with chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) demonstrate that elevated Bax/Bcl-2 ratios correspond with increased overall survival (OS) and extended progression-free survival (PFS), indicating enhanced sensitivity to apoptosis-inducing<sup>28,29</sup>. These findings suggest that the Bax/Bcl-2 ratio not only reflects apoptotic status at the molecular level but also carries direct clinical relevance for patient outcomes.

In the nervous system, an imbalance in the Bax/Bcl-2 ratio contributes to neuronal death under oxidative stress. An increase in Bax expression or a decrease in Bcl-2 levels triggers mitochondrial outer membrane permeabilization, release of cytochrome c, and activation of caspases, thereby accelerating neurodegenerative processes. This has been observed in various models of Alzheimer’s and Parkinson’s diseases, supporting the role of the Bax/Bcl-2 ratio as a key marker of neuronal vulnerability to programmed cell death<sup>27,29</sup>. In renal tissue, elevated Bax relative to Bcl-2 represents a characteristic response to acute kidney injury (AKI), indicating engagement of the intrinsic mitochondrial apoptotic cascade in tubular cells. Downregulated Bcl-2 expression combined with increased Bax expression initiate mitochondrial outer membrane permeabilization (MOMP), release of cytochrome c into the cytoplasm, and caspase-3 activation, eventually resulting in apoptosis. This observation is consistent with studies showing that higher Bax/Bcl-2 ratios are associated with increased tubular cell apoptosis following AKI<sup>30</sup>.

Collectively, these consistent findings across tissues and disease conditions highlight the Bax/Bcl-2 ratio as a “golden marker” of apoptosis, capable of quantitatively and functionally representing the apoptotic state. A high ratio promotes apoptosis, while a low ratio reflects resistance to programmed cell death. Therefore, monitoring and modulating the Bax/Bcl-2 ratio are crucial not only for understanding apoptotic mechanisms but also for developing therapeutic interventions aimed at enhancing apoptosis sensitivity across various pathological conditions<sup>16,30</sup>.

### *Integration of Transcriptional and Post-Translational Regulation*

Bax and Bcl-2 levels are regulated through intricate gene transcription and post-translational mechanisms. Activation of p53 upregulates Bax expression, while the Akt/PI3K and NF-κB pathways promote Bcl-2 expression. Furthermore, post-translational modifications such as

phosphorylation of Bcl-2 at Ser70 and ubiquitination of Bax regulate their stability and activity (Deng et al., 2023; Liu et al., 2021). The interplay between these regulatory mechanisms maintains an appropriate Bax/Bcl-2 ratio, ensuring apoptosis occurs only in response to proper cellular stress stimuli<sup>16,19</sup>.

### ***MOMP and Apoptotic Pathway Activation***

The Bax/Bcl-2 ratio serves a central function in regulating mitochondrial membrane permeabilization (MOMP), an essential event in the intrinsic apoptotic cascade. Upon activation, Bax assembles into oligomers that create channels in the mitochondrial membrane, facilitating cytochrome c release and subsequent assembly of the apoptosome, which activates caspase-9 and caspase-3 to execute apoptosis. Bcl-2 counteracts these events by binding Bax and inhibiting membrane permeabilization. Therefore, the relative levels of Bax and Bcl-2 serve as a primary determinant for triggering apoptotic signaling<sup>30</sup>.

### ***Clinical Relevance and Therapeutic Implications***

Alterations in the Bax/Bcl-2 ratio have profound clinical implications. Tumor cells with a low ratio often exhibit resistance to chemotherapy and radiotherapy, while increasing this ratio enhances responsiveness to apoptosis-inducing therapies<sup>31</sup>. Modern therapeutic approaches aim to modulate the Bax/Bcl-2 ratio by targeting its transcriptional and post-translational regulation such as activating p53, employing BH3 mimetics, or inhibiting Akt/Bcl-2 signaling to increase apoptosis sensitivity<sup>28,32</sup>. Therefore, the Bax/Bcl-2 ratio serves not only as a mechanistic indicator of apoptosis but also as a diagnostic, prognostic, and therapeutic biomarker solidifying its status as the *golden marker* in determining cell fate across various clinical contexts.

## **CONCLUSION**

In summary, the Bax/Bcl-2 ratio serves as a key molecular indicator of apoptosis, reflecting the delicate balance that governs cellular fate. Its regulation occurs at multiple levels, including transcriptional, translational, and post-translational modifications, highlighting its critical role as both a mechanistic hallmark and a clinical biomarker. A deeper understanding of this golden marker is expected to pave the way for novel diagnostic and therapeutic strategies targeting apoptosis-related diseases.

## **Competing Interests**

The authors declare that there are no conflicts of interest related to this work.

## **Authors' Contributions**

All authors contributed equally to this research, including conceptualization, data acquisition and analysis, literature review, manuscript preparation, and revision.

## **REFERENCES**

1. Bej, E., Cesare, P., Volpe, A. R., D'Angelo, M., & Castelli, V. (2024). Oxidative Stress and Neurodegeneration: Insights and Therapeutic Strategies for Parkinson's Disease. *Neurology International*, 16(3), 502–517. <https://doi.org/10.3390/neurolint16030037>
2. Cahyadi, A., Ugrasena, I. D., Andarsini, M., Larasati, M., Aryati, A., & Arumsari, D. (2022).

- Relationship between Bax and Bcl-2 Protein Expression and Outcome of Induction Phase Chemotherapy in Pediatric Acute Lymphoblastic Leukemia. *Asian Pacific Journal of Cancer Prevention*, 23(5), 1679–1685. <https://doi.org/10.31557/APJCP.2022.23.5.1679>
3. Fekry, G., Hamdy, M., El Razazz, M., & Hafez, H. (2024). AML-350 Role of Protein BAX and BCL-2 in the Prognosis of Acute Myeloid Leukemia in Adults. *Clinical Lymphoma Myeloma and Leukemia*, 24, S308. [https://doi.org/10.1016/S2152-2650\(24\)01188-1](https://doi.org/10.1016/S2152-2650(24)01188-1)
  4. Green, D. R. (2022). The Mitochondrial Pathway of Apoptosis. *Cold Spring Harbor Perspectives in Biology*, 14(5), a041038. <https://doi.org/10.1101/cshperspect.a041038>
  5. Habib, T. N., Altonsy, M. O., Ghanem, S. A., Salama, M. S., & Hosny, M. A. (2024). Optimizing combination therapy in prostate cancer: mechanistic insights into the synergistic effects of Paclitaxel and Sulforaphane-induced apoptosis. *BMC Molecular and Cell Biology*, 25(1), 5. <https://doi.org/10.1186/s12860-024-00501-z>
  6. Helaly, N. A., Esheba, N. E., Ammo, D. E. A., Elwan, N. M., & Elkholy, R. A. (2021). High Bax/Bcl-2 ratio is associated with good prognosis and better survival in patients with B cell chronic lymphocytic leukemia. *Leukemia Research*, 107, 106604. <https://doi.org/10.1016/j.leukres.2021.106604>
  7. Jedram, O., Maphanao, P., Karnchanapandh, K., Mahalapbutr, P., Thanan, R., & Sakonsinsiri, C. (2024). Corosolic Acid Induced Apoptosis via Upregulation of Bax/Bcl-2 Ratio and Caspase-3 Activation in Cholangiocarcinoma Cells. *ACS Omega*, 9(1), 1278–1286. <https://doi.org/10.1021/acsomega.3c07556>
  8. Jiang, Y., Fang, B., Xu, B., & Chen, L. (2020). The RAS-PI3K-AKT-NF-κB pathway transcriptionally regulates the expression of BCL2 family and IAP family genes and inhibits apoptosis in fibrous epulis. *Journal of Clinical Laboratory Analysis*, 34(3). <https://doi.org/10.1002/jcla.23102>
  9. Ke, D., Yu, Y., Li, C., Han, J., & Xu, J. (2022). Phosphorylation of BCL2 at the Ser70 site mediates RANKL-induced osteoclast precursor autophagy and osteoclastogenesis. *Molecular Medicine*, 28(1), 22. <https://doi.org/10.1186/s10020-022-00449-w>
  10. Kunac, N., Filipović, N., Kostić, S., & Vukojević, K. (2022). The Expression Pattern of Bcl-2 and Bax in the Tumor and Stromal Cells in Colorectal Carcinoma. *Medicina*, 58(8), 1135. <https://doi.org/10.3390/medicina58081135>
  11. Kuwana, T., King, L. E., Cosentino, K., Suess, J., Garcia-Saez, A. J., Gilmore, A. P., & Newmeyer, D. D. (2020). Mitochondrial residence of the apoptosis inducer BAX is more important than BAX oligomerization in promoting membrane permeabilization. *Journal of Biological Chemistry*, 295(6), 1623–1636. <https://doi.org/10.1074/jbc.RA119.011635>
  12. Li, K., van Delft, M. F., & Dewson, G. (2021). Too much death can kill you: inhibiting intrinsic apoptosis to treat disease. *The EMBO Journal*, 40(14). <https://doi.org/10.15252/emj.2020107341>
  13. Liu, N., Liu, Y., Wang, Y., Feng, C., Piao, M., & Liu, M. (2025). Oxidative cell death in the central nervous system: mechanisms and therapeutic strategies. *Frontiers in Cell and Developmental Biology*, 13. <https://doi.org/10.3389/fcell.2025.1562344>
  14. Liu, R., Chen, Y., Liu, G., Li, C., Song, Y., Cao, Z., Li, W., Hu, J., Lu, C., & Liu, Y. (2020). PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. *Cell Death & Disease*, 11(9), 797. <https://doi.org/10.1038/s41419-020-02998-6>

15. Mustafa, M., Ahmad, R., Tantry, I. Q., Ahmad, W., Siddiqui, S., Alam, M., Abbas, K., Moinuddin, Hassan, M. I., Habib, S., & Islam, S. (2024). Apoptosis: A Comprehensive Overview of Signaling Pathways, Morphological Changes, and Physiological Significance and Therapeutic Implications. *Cells*, 13(22), 1838. <https://doi.org/10.3390/cells13221838>
16. Nössing, C., & Ryan, K. M. (2023). 50 years on and still very much alive: ‘Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics.’ *British Journal of Cancer*, 128(3), 426–431. <https://doi.org/10.1038/s41416-022-02020-0>
17. Palabiyik, A. (2025). The role of Bcl-2 in controlling the transition between autophagy and apoptosis (Review). *Molecular Medicine Reports*, 32(1), 1–9. <https://doi.org/10.3892/mmr.2025.13537>
18. Pravdic, Z., Vukovic, N. S., Gasic, V., Marjanovic, I., Karan-Djurasevic, T., Pavlovic, S., & Tosic, N. (2023). The influence of BCL2, BAX, and ABCB1 gene expression on prognosis of adult de novo acute myeloid leukemia with normal karyotype patients. *Radiology and Oncology*, 57(2), 239–248. <https://doi.org/10.2478/raon-2023-0017>
19. Qian, S., Wei, Z., Yang, W., Huang, J., Yang, Y., & Wang, J. (2022). The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. *Frontiers in Oncology*, 12. <https://doi.org/10.3389/fonc.2022.985363>
20. Roufayel, R., Younes, K., Al-Sabi, A., & Murshid, N. (2022). BH3-Only Proteins Noxa and Puma Are Key Regulators of Induced Apoptosis. *Life*, 12(2), 256. <https://doi.org/10.3390/life12020256>
21. Sabet, N., Soltani, Z., Khaksari, M., Iranpour, M., Afshar, R. M., Mehdiabadi, F. M., & Raji-Amirhasani, A. (2022). The effect of two types of diet on apoptosis indexes, lipid profile and histopathological outcome in acute kidney injury during exercise. *BMC Nephrology*, 23(1), 315. <https://doi.org/10.1186/s12882-022-02938-w>
22. Sadati, S., Khalaji, A., Bonyad, A., Khoshdooz, S., Hosseini Kolbadi, K. S., Bahrami, A., Moeinfar, M. S., Morshedi, M., Ghamsaraian, A., Eterafi, M., Eshraghi, R., Khaksary Mahabady, M., & Mirzaei, H. (2025). NF-κB and apoptosis: colorectal cancer progression and novel strategies for treatment. *European Journal of Medical Research*, 30(1), 616. <https://doi.org/10.1186/s40001-025-02734-w>
23. Saddam, M., Paul, S. K., Habib, M. A., Fahim, M. A., Mimi, A., Islam, S., Paul, B., & Helal, M. M. U. (2024). Emerging biomarkers and potential therapeutics of the BCL-2 protein family: the apoptotic and anti-apoptotic context. *Egyptian Journal of Medical Human Genetics*, 25(1), 12. <https://doi.org/10.1186/s43042-024-00485-7>
24. Singh, R., Letai, A., & Sarosiek, K. (2019). Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nature Reviews Molecular Cell Biology*, 20(3), 175–193. <https://doi.org/10.1038/s41580-018-0089-8>
25. Suraweera, C. D., Hinds, M. G., & Kvansakul, M. (2020). Poxviral Strategies to Overcome Host Cell Apoptosis. *Pathogens*, 10(1), 6. <https://doi.org/10.3390/pathogens10010006>
26. Tang, V., & Wang, J. F. (2014). Mitochondrial dysfunction and oxidative stress in bipolar disorder. *Systems Biology of Free Radicals and Antioxidants*, 9783642300, 2411–2429. [https://doi.org/10.1007/978-3-642-30018-9\\_83](https://doi.org/10.1007/978-3-642-30018-9_83)
27. Tian, X., Srinivasan, P. R., Tajiknia, V., Sanchez Sevilla Uruchurtu, A. F., Seyhan, A. A., Carneiro, B. A., De La Cruz, A., Pinho-Schwermann, M., George, A., Zhao, S., Strandberg,

- J., Di Cristofano, F., Zhang, S., Zhou, L., Raufi, A. G., Navaraj, A., Zhang, Y., Verovkina, N., Ghandali, M., ... El-Deiry, W. S. (2024). Targeting apoptotic pathways for cancer therapy. *Journal of Clinical Investigation*, 134(14). <https://doi.org/10.1172/JCI179570>
28. Üremiş, N., & Üremiş, M. M. (2025). Oxidative/Nitrosative Stress, Apoptosis, and Redox Signaling: Key Players in Neurodegenerative Diseases. *Journal of Biochemical and Molecular Toxicology*, 39(1). <https://doi.org/10.1002/jbt.70133>
29. Vogler, M., Braun, Y., Smith, V. M., Westhoff, M.-A., Pereira, R. S., Pieper, N. M., Anders, M., Callens, M., Vervliet, T., Abbas, M., Macip, S., Schmid, R., Bultynck, G., & Dyer, M. J. (2025). The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy. *Signal Transduction and Targeted Therapy*, 10(1), 91. <https://doi.org/10.1038/s41392-025-02176-0>
30. Wei, H., Wang, H., Wang, G., Qu, L., Jiang, L., Dai, S., Chen, X., Zhang, Y., Chen, Z., Li, Y., Guo, M., & Chen, Y. (2023). Structures of p53/BCL-2 complex suggest a mechanism for p53 to antagonize BCL-2 activity. *Nature Communications*, 14(1), 4300. <https://doi.org/10.1038/s41467-023-40087-2>
31. Yi, X., Wei, R., Huang, S., Wei, P., Li, H., Li, Z., Aschner, M., Jiang, Y., Ou, S., & Li, S. (2025). The effect of resveratrol on lead-induced oxidative damage and apoptosis in HT-22 cells. *Food and Chemical Toxicology*, 197, 115274. <https://doi.org/10.1016/j.fct.2025.115274>
32. Zhang, Z., Hou, L., Liu, D., Luan, S., Huang, M., & Zhao, L. (2024). Directly targeting BAX for drug discovery: Therapeutic opportunities and challenges. *Acta Pharmaceutica Sinica B*, 14(6), 2378–2401. <https://doi.org/10.1016/j.apsb.2024.02.010>