International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2024.166.173

Research Article
Inhibition of Multiple Myeloma Growth by Wogonin Involves Mitochondrial Apoptosis and G2/M Cycle Arrest

[1]Ling He, [1]Hongwei Wu, [2]Zhiqiang Sun and [3]Jie Zhang

[1]Department of Hematology, The First Affiliated Hospital of Chengdu Medical College, 610599 Chengdu, Sichuan, China
[2]Department of Hematology, Shenzhen Hospital of Southern Medical University, 518000 Shenzhen, Guangdong, China
[3]Department of Neurosurgery, The First Affiliated Hospital of Chengdu Medical College, 610599 Chengdu, Sichuan, China

Abstract

Background and Objective: Wogonin belongs to active flavonoids and has been reported with several biological and pharmacological potentials. Wogonin has been reported with anticancer activity along with other biological applications. The anticancer effects of wogonin are mediated via its mitochondrial apoptosis and G2/M cycle arrest. Therefore, wogonin was herein testified for inhibition of multiple myeloma (MM) growth involving mitochondrial apoptosis and G2/M cycle arrest. **Materials and Methods:** The MTT assay was employed to test the cellular viability of MM cells. Apoptosis estimations were performed with Annexin V/PI staining assay, AO/EB staining assay and western blotting assay. The cell cycle in MM cells was analysed through flow cytometry. **Results:** The wogonin treatment on multiple melanoma cells induced anti-viability effects in a dose-reliant fashion. Moreover, it was shown that the anti-viability properties of wogonin are facilitated by its ability to induce apoptosis. According to the study's results, the wogonin treatment led to a dose-dependent cell cycle arrest in the G2/M phase, as verified by cell cycle monitoring. **Conclusion:** The wogonin-induced inhibition of MM growth involves mitochondrial apoptosis and G2/M cycle arrest. Therefore, it can prove a leading candidate in MM research and treatment provided further investigations.

Key words: Multiple myeloma, flavonoids, wogonin, mitochondrial apoptosis, G2/M cycle arrest

Citation: He, L., H. Wu, Z. Sun and J. Zhang, 2024. Inhibition of multiple myeloma growth by wogonin involves mitochondrial apoptosis and G2/M cycle arrest. Int. J. Pharmacol., 20: 166-173.

Corresponding Author: Jie Zhang, Department of Neurosurgery, The First Affiliated Hospital of Chengdu Medical College, 610500 Chengdu, Sichuan, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hematopoietic tumors are classified into two groups: Lymphoma and myeloma[1]. Myeloma is a lethal distortion arising from the malignant proliferation of B-cell lineage-bearing neoplastic plasma cells. These cells reside within the bone marrow and their uncontrolled proliferation results in the overproduction of immunoglobulin and plasma paraprotein[2]. This malignancy primarily involves bone, but in some cases, skin and lymph nodes also get infected. Multiple myeloma (MM) is a dangerous and incurable medical condition, but by using appropriate treatment, its lethal symptoms can be suppressed. Mostly, MM occurs in marrow-containing bones, including the femur, pelvis and vertebrae. Various epidemiological studies have reported that in the Western world, MM is the 2nd most frequent haematological malignancy, accounting for around 1% of cancer-related fatalities[3]. In the UK alone, 80 people per million per year suffer from MM[4]. The MM shows geographical variation as North America, Europe and Australia witness the maximum cases[5]. Aetiological investigations of MM bear poor responses and understanding. Some of the studies have testified that environmental and occupational risk factors are responsible for MM development, including ionizing radiation, petroleum, farming and asbestos[6]. Studies regarding familial MM have reported hereditary causes and the accumulation of genetic mutations in immunoglobulins produced by mutant plasma cells[7,8]. The MM has been described as a harmful malignancy that needs to be addressed with novel and effective drugs that can lead to the complete elimination of MM cells.

Flavonoids are a prominent category of polyphenolic chemicals found naturally as secondary metabolites in plants. Phytochemicals are accountable for the fragrance and pigmentation of flowers. Flavonoids have notable biological and therapeutic uses, such as anti-inflammatory, anti-allergic, antioxidant, antiviral and antibacterial properties[9-11]. Flavonoids affect several signal transduction pathways in cancer, leading to the prevention of metastasis, angiogenesis, proliferation and increased apoptosis[12]. Wogonin is among the active flavonoids and is a potential Mcl-1 (Myeloid Cell Leukemia 1) and Bcl-2 (B-Cell Lymphoma 2) inhibitor in variant cancers[13,14]. Recent investigations have shown evidence that wogonin has anticancer action by triggering apoptosis, particularly at a very high maximum-tolerated dosage[15,16]. In pancreatic cancer, wogonin has shown anticancer potential via inhibition of the NF-κB (nuclear factor) and Mcl-1 pathways[17,18]. This investigation intended to determine whether wogonin could prevent the development of MM. This inhibitory mechanism includes mitochondrial apoptosis and cell cycle arrest in the G2/M phase.

MATERIALS AND METHODS

Study area: The current investigation was conducted at The First Affiliated Hospital of Chengdu Medical College from June to August, 2023.

Cytotoxicity assay: In this investigation, the cytotoxic effects of wogonin against B lymphocyte cells (IM9) and normal B cells were determined by an MTT assay. These B lymphocyte cells (IM9) and normal B cells were obtained from the American Type Culture Collection (ATCC) centre. The IM9 and normal B cells (1×10^5) were placed onto 96-well plates and pre-cultured in growth medium RPMI with 10% fetal bovine serum (FBS) through 24 hrs of incubation at 37°C in a CO_2 (5%) incubator. Afterward, cells were first treated for 2 hrs with sterile water and then drug treatment (wogonin) was initiated. Both cell types were treated with different doses of wogonin, viz 1.25, 2.5, 5, 10, 20, 40, 80 and 160 µM; in the case of controls, DMSO (0.1%) was used for 24 hrs. Thereafter, the media was removed and washing was accomplished with PBS. The MTT (10 µL) solution was then applied to each well of 96-well plates and incubated at 37°C for 1.5 hrs. Finally, optical density was measured by monitoring absorbance at 450 nm.

Apoptosis assessment: After treatment with sterile water for 2 hrs, IM9 cells were subjected to wogonin exposure for 24 hrs at changing doses viz 0, 3.5, 7 and 14 µM. Afterwards, cells were harvested and washing was performed three times with PBS. Subsequently, the cells that had undergone treatment were reintroduced in a binding buffer consisting of 10 mM HEPES/NaOH pH 7.4, 140 mM NaCl and 2.5 mM $CaCl_2$. Subsequently, 5 µL of Annexin V fluorescein isothiocyanate and propidium iodide were added, both of which were sourced from the Beyotime Institute of Biotechnology. Finally, the samples were subjected to analysis using a FACSCalibur flow cytometer (BD Biosciences, located in New Jersey, USA).

AO/EB staining assay for determination of apoptosis: Cancerous IM9 cells were harvested at 80% growth confluence, followed by wogonin drug exposure. Wogonin was applied with varying doses, viz 0, 3.5, 7 and 14 µM, in DMEM for 24 hrs carrying FBS (10%) in an atmosphere of CO_2 (5%) at 37°C. Subsequently, cells treated with wogonin underwent three washes with PBS, followed by fixation with

paraformaldehyde (4%) for about 20 min. Then staining was performed with AO/EB staining solutions (bearing 1 mg L^{-1} of each) at 37°C for 10 min. Afterward, the cells were seen and imaged by a fluorescent microscope (Nikon TE2000; Nikon Corporation, Japan).

Cell cycle analysis: The double thymidine block method was used for the synchronisation of IM9 cancerous cells[19]. In brief, cells were cultured with the first block (2 mM thymidine) for 14 hrs and they were discharged. After 10 hrs, cells were again blocked with thymidine (second block) for 14 hrs. Following that, cells were treated with varied wogonin concentrations of 0, 3.5, 7 and 14 µM for 24 hrs. The PI staining was used to determine the DNA content for cell cycle assessments. Cells were rinsed in PBS before being fixed in ethanol. These cells were subsequently rinsed twice with PBS before being incubated with RNase (0.5 mg mL^{-1}) and stained with PI. The PI-DNA complex-emitted fluorescence was then quantified using flow cytometry (BD Biosciences, United States).

Western blotting assay: After wogonin treatment at varying doses of 0, 3.5, 7 and 14 µM for 24 hrs, IM9 cells were lysed with lysis buffer (Beyotime, China). Afterward, a bicinchoninic acid assay was used to quantify protein content within each lysate. Sodium Dodecyl Sulfate-Polyacrylamide Gel (SDS-PAG (10%)) was loaded with equal protein contents. Following that, proteins were shifted to microporous PVDF membranes for blotting utilizing rabbit anti-human primary antibodies. The following antibodies were used, rabbit anti-human Bax monoclonal antibody, caspase-3 poly-clonal antibody, Bcl-2 monoclonal antibody, Poly-ADP Ribose Polymerase (PARP), LC3-I, LC3-II, p62 and Beclin-1 (1:1000 dilution; Cell Signaling Technology, United States). Thereafter, secondary antibody treatment was given overnight at 4°C using horseradish peroxidase-conjugated anti-rabbit secondary antibody. Finally, the ECL (enhanced chemiluminescence) substrate (Pierce, United States) was used for visualization of protein bands.

Statistical analysis: The SPSS 19.0 software tool (IBM SPSS, New York, United States) was utilized to evaluate the data obtained from triplicate experiments and presented as Mean±Standard Deviation. The variance was assessed at a threshold level of $p<0.05$.

RESULTS

Wogonin-induced cytotoxicity in IM9 cells: Several compounds have been reported to show cytotoxicity against human cancers, but they inhibit the viability of normal B cells too. Thus, limiting their use and applications in cancer chemotherapy. Wogonin (Fig. 1a) was tested for its cytotoxicity against normal B cells and cancerous IM9 cells. The MTT experiment was implemented to discover the

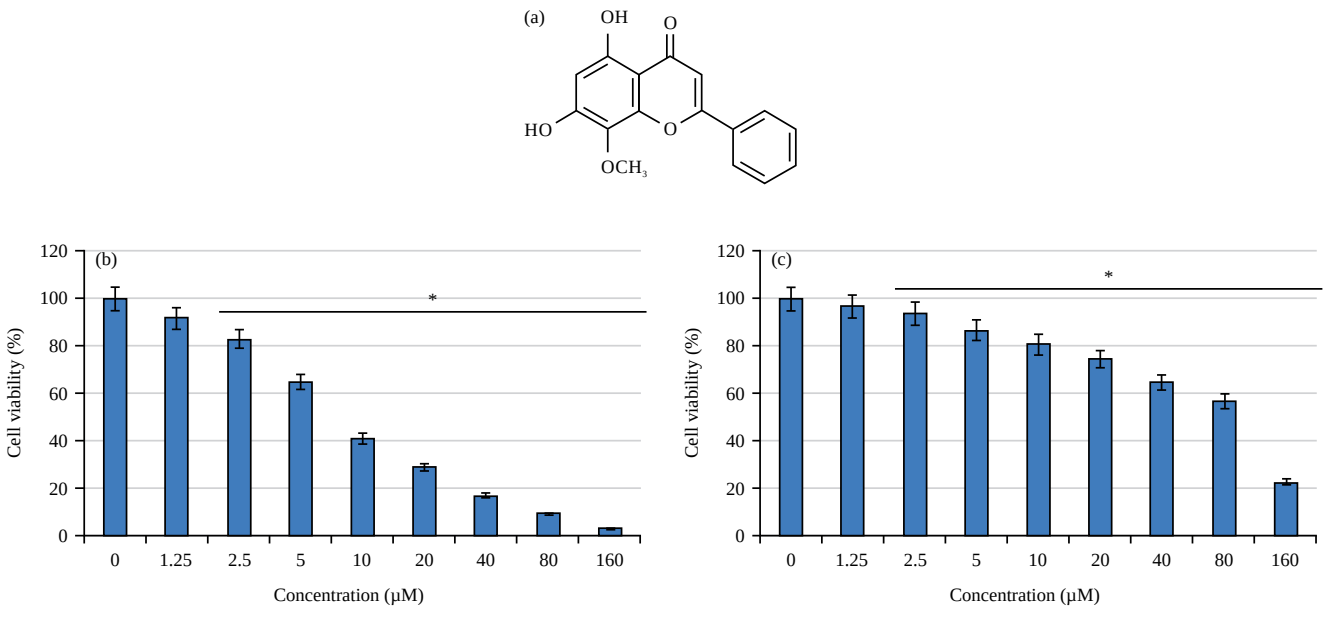

Fig. 1(a-c): (a) Chemical structure of wogonin flavonoid, (b) Cellular viability of IM9 cells was exposed to wogonin for 24 hrs at various concentrations and (c) Cellular viability of normal B cells after wogonin exposure for 24 hrs at indicated doses
Data represent the Means±SD, variance was assessed at a threshold level of *$p<0.05$ against controls and individual experiment repetitions (n) = 3

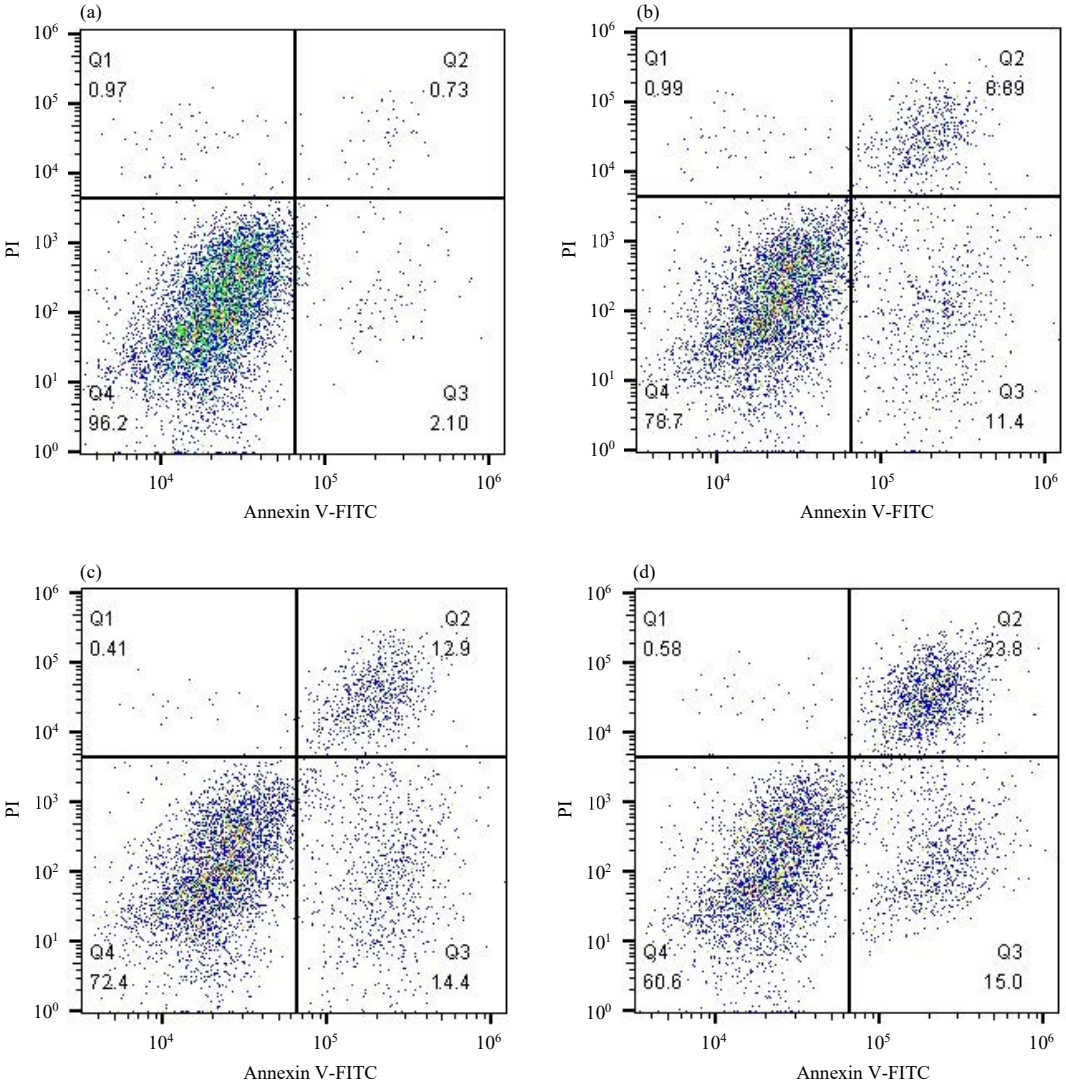

Fig. 2(a-d): Flow cytometric analysis of apoptosis after examination of wogonin treated IM9 cells through Annexin V/PI staining assay, (a) Control, (b) 3.5 μM, (c) 7 μM and (d) 14 μM

Results presented increased IM9 apoptotic cell percentage after drug treatment as compared to controls. Data represent the Means±SD, $p<0.05$ against controls and n = 3

cytotoxicity of the wogonin drug against MM. Results indicated the immense potential of wogonin in inhibiting the viability and potency of cancerous IM9 cells. The viability was observed to reduce from 100% to almost 5% after increasing wogonin doses from 0-160 μM (Fig. 1b). Normal B cell viability remained almost the same on application of the wogonin drug (Fig. 1c). Therefore, it was depicted from MTT results that wogonin has a great potential to inhibit IM9 cell viability.

Wogonin exhibits apoptosis-inducing potential in IM9 cells: In the past three decades, apoptosis has been a breakthrough in cancer research and has evolved several allied pathways as therapeutic targets. Wogonin was tested for its apoptosis-inducing capability against IM9 cells. After 24 hrs of exposure to different wogonin dosages (0-160 μM), IM9 cells were stained with Annexin V/PI to assess apoptosis. Outcomes showed that the IM9 apoptotic cell percentage increased from 3% in controls to 38% after exposure to higher drug concentrations (Fig. 2). Therefore, it was evidenced that the cytotoxicity of the wogonin drug is mediated through apoptosis. An AO/EB staining assessment was also done to examine the morphology of apoptotic cells. Images indicated that the number of apoptotic cells rose with increasing dosages, as did condensed nuclei, cell shrinkage,

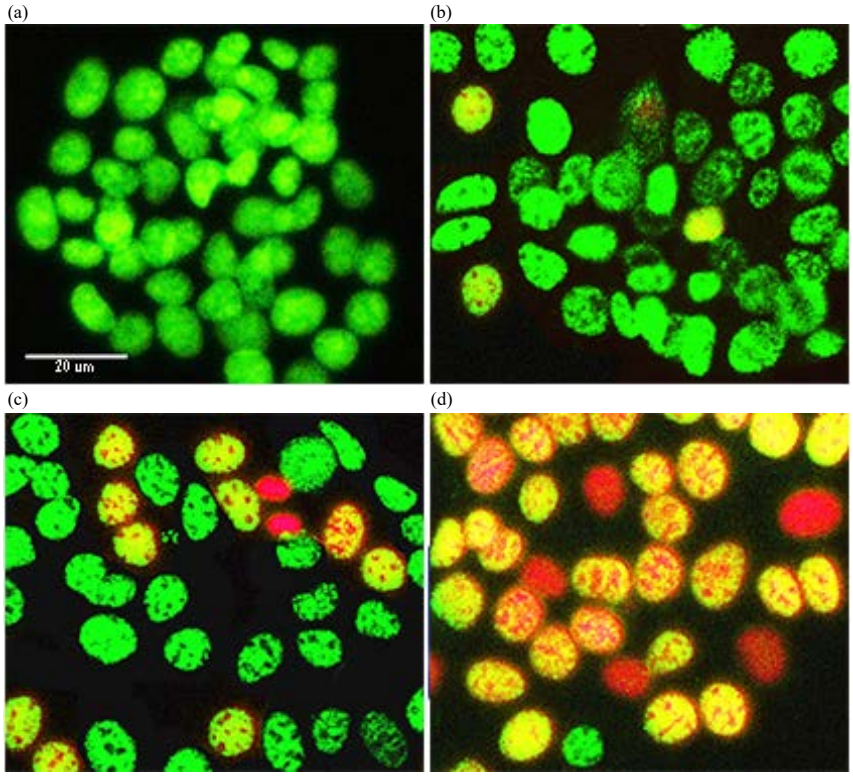

Fig. 3(a-d): Pictures representing AO/EB-stained cells after treatment with wogonin at indicated doses, (a) Control, (b) 3.5 μM, (c) 7 μM and (d) 14 μM
Results indicate increased apoptotic cell percentage and n = 3

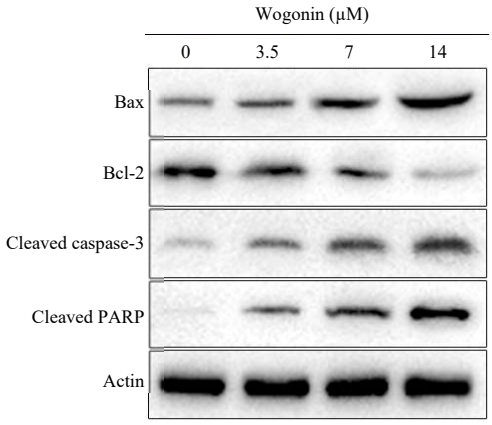

Fig. 4: Western blot assay presenting expressions of anti-and pro-apoptosis proteins after wogonin treatment at represented doses
n = 3

DNA fragmentation and membrane blebbing (Fig. 3). Thus, indicating the initiation of apoptosis by the wogonin drug in IM9 cells. Western blotting assay was performed to check the activity of pro and anti-apoptotic proteins. The outcomes demonstrated elevated levels of cleaved PARP, caspase-3 and BAX proteins, whereas anti-apoptotic Bcl-2 protein levels were considerably decreased by wogonin administration to IM9 cells (Fig. 4).

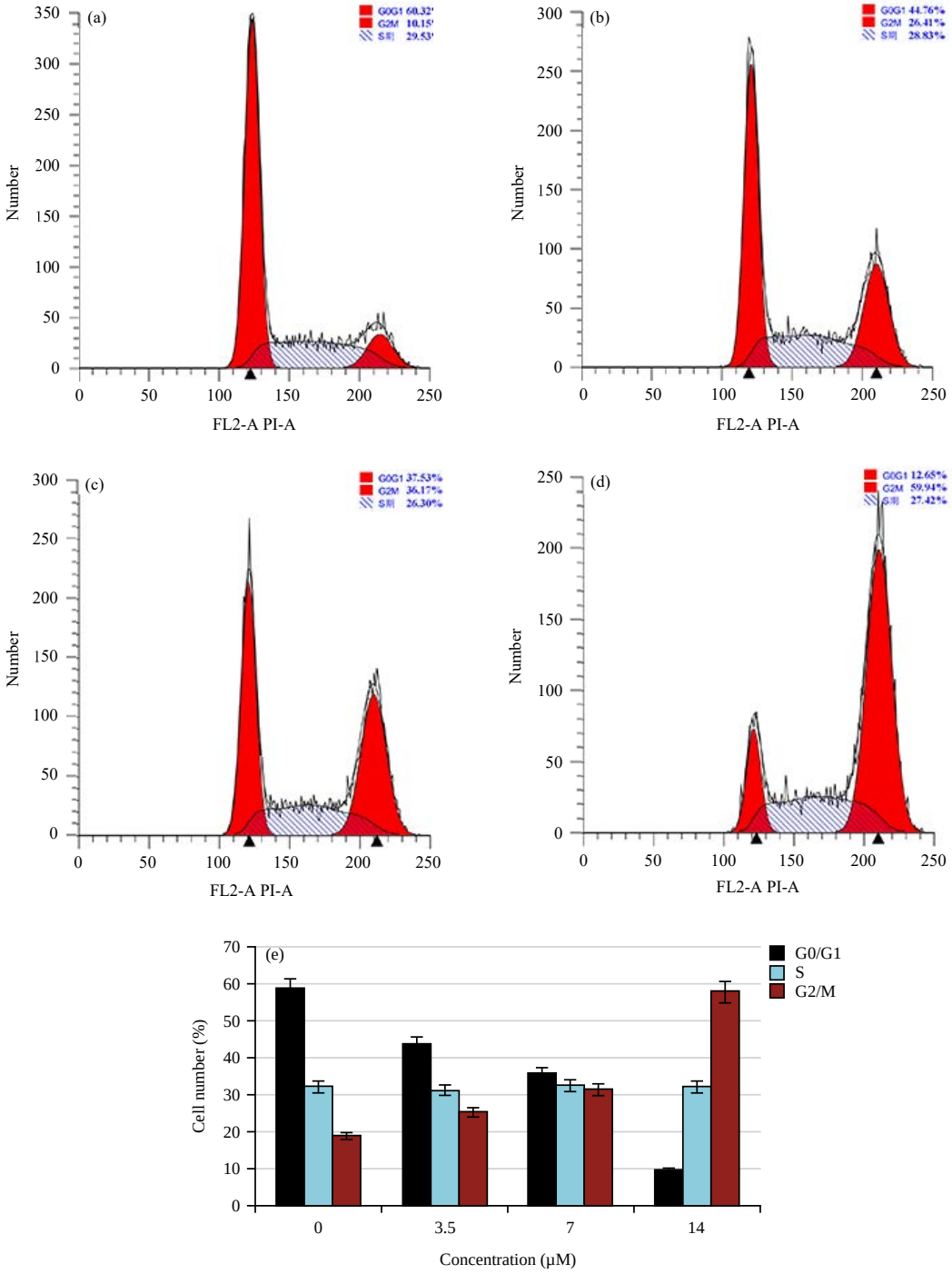

Fig. 5(a-e): Flow cytometric analysis of wogonin-treated IM9 cells after PI staining, (a) Control, (b) 3.5 μM, (c) 7 μM, (d) 14 μM and (e) Concentration of G0/G1, S-phase and G2/M

Results representing increased G2/M-phase cells parallel to drug treatment, Data represent the Means±SD, $p<0.05$ against controls and n = 3

Wogonin-induced cell cycle arrest in IM9 cells: Frequent proliferation is a dominant feature of cancer cells. Targeting the cell cycle in cancer chemotherapy has proven better results in the past two or three decades. Herein, wogonin was investigated for cell cycle inhibition through flow cytometry. Results indicated that S-phase and G0/G1-phase cells reduced normally with increased drug doses, but the G2/M-phase cells increased. The G2/M-phase cells increased from almost 15% to about 60% after drug exposure (0-160 μM) (Fig. 5).

DISCUSSION

Consequently, the present research was conducted to examine the suppressive effects of wogonin on the development of MM. This investigation specifically focuses on the mechanisms of mitochondrial apoptosis and G2/M cell cycle arrest. The results from the MTT assay indicated that wogonin is a potential cell viability inhibitor against IM9 cells. Further, the antiproliferative effects of wogonin in IM9 cells were found to be due to apoptosis and autophagy induction, as revealed by Annexin V/PI staining and TEM analysis, respectively. The expressions of pro-apoptosis proteins were observed to increase with increasing wogonin doses in IM9 cells. In addition to this, wogonin blocked the cell cycle in IM9 cells at the G2/M phase, as revealed by the flow cytometric analysis. The word "apoptosis" was chosen to explain a certain type of cell death that is associated with specific morphological changes. The observed phenomena include chromosomal DNA breakage, chromatin condensation, nuclear fragmentation, cell shrinkage and membrane blebbing[20-22]. Apoptosis is of two types, depending on the activating signals; extrinsic and intrinsic. Intrinsic apoptosis is stimulated by internal factors (mitochondria-mediated) and extrinsic apoptosis is activated through death receptors. The first modulatory step, intrinsic apoptosis, is facilitated by the Bcl-2 family of proteins (anti-apoptotic proteins)[23,24]. Studies have reported overexpression of Bcl-2 through chromosomal translocation in follicular B-cell limphomas[25,26]. The Bcl-2 proteins are termed pro-survival proteins and an opposite functional group of pro-apoptotic BH123 proteins (Bax and Bak) has been recognised[27]. The Bcl-2 family proteins form heterodimers with Bak and Bax in the absence of apoptotic stress and maintain the MM (outer mitochondria membrane), thus blocking apoptosis through mitochondria[28]. In the context of apoptotic stress, an increase in the levels of BH3-only proteins occurs, leading to their interaction with Bcl-2 proteins[29]. This process enables the release of pro-apoptotic proteins from their inhibitory state. Released Bax/Bak form oligomers that form channels in and release cytochrome c into the cytoplasm. Cytochrome c initiates caspase cascade and ultimately apoptosis[30]. Wogonin molecules have been reported to have apoptosis-inducing potential against different human cancers[31,32].

CONCLUSION

The experiments undertaken in the present investigation have shown that the wogonin flavonoid has promising potential as an anticancer drug targeting human MM. The inhibition of MM growth by wogonin involves mitochondrial apoptosis, autophagy and G2/M cycle arrest. Therefore, wogonin can be considered for MM management, but further *in vitro* and *in vivo* studies are recommended.

SIGNIFICANCE STATEMENT

Wogonin is classified as an active flavonoid and has been shown to possess several biological and pharmacological properties. Nevertheless, the current body of research regarding the anticancer properties of wogonin is limited. Consequently, the present study aims to investigate the efficacy of wogonin in suppressing the development of multiple myeloma (MM) by examining its impact on mitochondrial apoptosis and G2/M cell cycle arrest. Based on the results obtained from the research, it can be inferred that the wogonin flavonoid has considerable promise as a pharmacological agent for combating cancer, namely in its ability to selectively target human MM cells. The growth of MM is suppressed by wogonin via the induction of mitochondrial apoptosis, autophagy and G2/M cell cycle arrest. Hence, it is plausible to consider wogonin as a potential candidate for the treatment of MM. However, it is advisable to conduct further *in vitro* and *in vivo* investigations to further evaluate its efficacy and safety.

ACKNOWLEDGMENT

The authors would like to thank the higher authorities for the facilities offered.

REFERENCES

1. Xie, S., J. Li, J.H. Wang, Q. Wu and P. Yang *et al*., 2010. IL-17 activates the canonical NF-κB signaling pathway in autoimmune B cells of BXD2 mice to upregulate the expression of regulators of G-protein signaling 16. J. Immunol., 184: 2289-2296.
2. Vail, D.M., D.H. Thamm and J.M. Liptak, 2019. Hematopoietic Tumors. In: Withrow and MacEwen's Small Animal Clinical Oncology, Vail, D.M., D.H. Thamm and J.M. Liptak (Eds.), Saunders, United States, ISBN: 9780323594967, pp: 688-772.
3. Fujino, M., 2018. The histopathology of myeloma in the bone marrow. J. Clin. Exp. Hematopathol., 58: 61-67.
4. Zhang, N., J. Wu, Q. Wang, Y. Liang and X. Li *et al*., 2023. Global burden of hematologic malignancies and evolution patterns over the past 30 years. Blood Cancer J., Vol. 13. 10.1038/s41408-023-00853-3.
5. Bird, S.A. and K. Boyd, 2019. Multiple myeloma: An overview of management. Palliative Care Social Pract., Vol. 13. 10.1177/1178224219868235.

6. Zhou, L., Q. Yu, G. Wei, L. Wang and Y. Huang *et al*., 2021. Measuring the global, regional, and national burden of multiple myeloma from 1990 to 2019. BMC Cancer, Vol. 21. 10.1186/s12885-021-08280-y.
7. Huh, D.A., M.S. Kang, J. Lee, J.Y. Choi, K.W. Moon and Y.J. Lee, 2021. Occupational and environmental asbestos exposure and the risk of lung cancer in Korea: A case-control study in South Chungcheong Province of Korea. PLoS ONE, Vol. 16. 10.1371/journal.pone.0249790.
8. Boyle, E.M., F.E. Davies, X. Leleu and G.J. Morgan, 2014. Understanding the multiple biological aspects leading to myeloma. Haematologica, 99: 605-612.
9. Prideaux, S.M., E.C. O'Brien and T.J. Chevassut, 2014. The genetic architecture of multiple myeloma. Adv. Hematol., Vol. 2014. 10.1155/2014/864058.
10. Panche, A.N., A.D. Diwan and S.R. Chandra, 2016. Flavonoids: An overview. J. Nutr. Sci., Vol. 5. 10.1017/jns.2016.41.
11. Asad Ullah, S. Munir, S.L. Badshah, N. Khan and L. Ghani *et al*., 2020. Important flavonoids and their role as a therapeutic agent. Molecules, Vol. 25. 10.3390/molecules25225243.
12. Roy, A., A. Khan, I. Ahmad, S. Alghamdi and B.S. Rajab *et al*., 2022. Flavonoids a bioactive compound from medicinal plants and its therapeutic applications. BioMed Res. Int., Vol. 2022. 10.1155/2022/5445291.
13. Abotaleb, M., S.M. Samuel, E. Varghese, S. Varghese, P. Kubatka, A. Liskova and D. Büsselberg, 2019. Flavonoids in cancer and apoptosis. Cancers, Vol. 11. 10.3390/cancers11010028.
14. Sulkshane, P. and T. Teni, 2022. Myeloid cell leukemia-1: A formidable barrier to anticancer therapeutics and the quest of targeting it. Explor. Targeted Antitumor Ther., 3: 278-296.
15. Young, A.I., P. Timpson, D. Gallego-Ortega, C.J. Ormandy and S.R. Oakes, 2018. Myeloid cell leukemia 1 (MCL-1), an unexpected modulator of protein kinase signaling during invasion. Cell Adhes. Migr., 12: 513-523.
16. Sharifi-Rad, J., J. Herrera-Bravo, L.A. Salazar, S. Shaheen and S.A. Ayatollahi *et al*., 2021. The therapeutic potential of wogonin observed in preclinical studies. Evidence-Based Complementary Altern. Med., Vol. 2021. 10.1155/2021/9935451.
17. Huynh, D.L., N. Sharma, A.K. Singh, S.S. Sodhi and J.J. Zhang *et al*., 2017. Anti-tumor activity of wogonin, an extract from *Scutellaria baicalensis*, through regulating different signaling pathways. Chin. J. Nat. Med., 15: 15-40.
18. Li, S.J., S.J. Sun, J. Gao and F.B. Sun, 2016. Wogonin induces Beclin-1/PI3K and reactive oxygen species-mediated autophagy in human pancreatic cancer cells. Oncol. Lett., 12: 5059-5067.
19. Liu, X., X. Peng, S. Cen, C. Yang, Z. Ma and X. Shi, 2023. Wogonin induces ferroptosis in pancreatic cancer cells by inhibiting the Nrf2/GPX4 axis. Front. Pharmacol., Vol. 14. 10.3389/fphar.2023.1129662.
20. Chen, G. and X. Deng, 2018. Cell synchronization by double thymidine block. Bio-Protocol, Vol. 8. 10.21769/BioProtoc.2994.
21. Moujalled, D., A. Strasser and J.R. Liddell, 2021. Molecular mechanisms of cell death in neurological diseases. Cell Death Differ., 28: 2029-2044.
22. Simões, A.E.S., D.M. Pereira, S.E. Gomes, H. Brito and T. Carvalho *et al*., 2015. Aberrant MEK5/ERK5 signalling contributes to human colon cancer progression via NF-κB activation. Cell Death Dis., Vol. 6. 10.1038/cddis.2015.83.
23. Takács-Vellai, K., 2023. Apoptosis and autophagy, different modes of cell death: How to utilize them to fight diseases? Int. J. Mol. Sci., Vol. 24. 10.3390/ijms241411609.
24. Jan, R. and G.E.S. Chaudhry, 2019. Understanding apoptosis and apoptotic pathways targeted cancer therapeutics. Adv. Pharm. Bull., 9: 205-218.
25. Cavalcante, G.C., A.P. Schaan, G.F. Cabral, M.N. Santana-da-Silva, P. Pinto, A.F. Vidal and Â. Ribeiro-dos-Santos, 2019. A cell's fate: An overview of the molecular biology and genetics of apoptosis. Int. J. Mol. Sci., Vol. 20. 10.3390/ijms20174133.
26. Klanova, M. and P. Klener, 2020. BCL-2 proteins in pathogenesis and therapy of B-cell non-hodgkin lymphomas. Cancers, Vol. 12. 10.3390/cancers12040938.
27. Zhu, Z., T. Li, X. Zhang, Z. Zhang and D. Zhu *et al*., 2020. Molecular and clinical progress in follicular lymphoma lacking the t(14;18) translocation (Review). Int. J. Oncol., 56: 7-17.
28. Shamas-Din, A., J. Kale, B. Leber and D.W. Andrews, 2013. Mechanisms of action of Bcl-2 family proteins. Cold Spring Harbor Perspect. Biol., Vol. 5. 10.1101/cshperspect.a008714.
29. Moldoveanu, T. and P.E. Czabotar, 2019. BAX, BAK, and BOK: A coming of age for the BCL-2 family effector proteins. Cold Spring Harbor Perspect. Biol., Vol. 12. 10.1101/cshperspect.a036319.
30. Kale, J., E.J. Osterlund and D.W. Andrews, 2018. BCL-2 family proteins: Changing partners in the dance towards death. Cell Death Differ., 25: 65-80.
31. Hussar, P., 2022. Apoptosis regulators Bcl-2 and caspase-3. Encyclopedia, 2: 1624-1636.
32. Tuli, H.S., P. Rath, A. Chauhan, G. Parashar and N.C. Parashar *et al*., 2023. Wogonin, as a potent anticancer compound: From chemistry to cellular interactions. Exp. Biol. Med., 248: 820-828.