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# *Mentha longifolia* L. Inhibits Colorectal Cancer Cell Proliferation and Induces Apoptosis via Caspase Regulation

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**Abstract:** Naturopathy or herbal medicine has been widely used as an alternative treatment for several illnesses, such as cancer, as they are generally acknowledged as a treatment with lesser side effects. This research evaluated the bioactive compounds profiling, antioxidant, and anticancer potential in *Mentha longifolia* L. (essential oil and extract), using different solvent polarities (hexane, methanol, and diethyl ether). Meanwhile, the caspase 3 gene expression and cell cycle status of methanolic extract were determined in colorectal cancer cells (Caco-2 and SW48). The overall findings showed that methanolic extraction exhibited the highest total phenolic and flavonoid with respective values of 59.25 mg GAE (Gallic acid) eq./g DW (dry weight) and 20.02 mg RE (Rutin) eq./g DW, respectively, compared to hexane and diethyl ether. Furthermore, piperitenone oxid and piperitonone were found to be the dominant volatile compounds in methanolic extracts and essential oils. Additionally, the methanolic extract possesses higher antioxidant and anticancer activities. The molecular analysis indicated that methanolic extract up-regulated the expression of caspase 3 and increased the SubG1 (method to detecting cell death) peaks in treated Caco-2 and SW48 cell lines. To conclude, *M. longifolia* L. could serve as an effective therapeutic agent and a remedy for several illnesses, such as cancer caused by oxidative stress.

**Keywords:** *Mentha longifolia* L.; antioxidants; apoptosis; gene expression; colorectal cancer



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## 1. Introduction

There has been a noticeable trend towards plant-based medicines for the last few years due to the high cost and increased risks associated with allopathic medicines. Plants have been used for medicinal purposes throughout history and have played an essential role in human health [1]. Most research in the 19th century mainly focused on secondary metabolites, which are compounds produced by plants through metabolic pathways derived from primary metabolic pathways. Secondary metabolites have been used as the foundation for many commercial pharmaceutical drugs and herbal remedies, and they are effective in treating diabetes, cancer, hypertension, anemia, and malaria [2,3]. Flavonoids and phenolics are examples of secondary metabolites with promising medical benefits [4,5]. Several new cytotoxic secondary metabolites are isolated from plants each year and constitute a source of new possibilities to explore to fight against cancerous diseases. However, some natural compounds cannot be used in clinical practice due to their physico-chemical properties (e.g., limited bioavailability) and/or their toxicity. On the other hand, plant-occurring

secondary metabolites can often be excellent leads for drug development. Overall, secondary metabolites of medicinal plants offer a promising area of research for developing new therapies for various diseases.

*Mentha longifolia* L. is a herb widely used in Southeast Asian countries to treat various ailments. Its essential oils and aerial parts have been used as a food preservative and a protective and curative alternative for treating many illnesses, including gastrointestinal and respiratory disorders, infectious diseases, and inflammatory diseases [6,7]. *M. longifolia* contains a large number of phenolic and flavonoid compounds, which have high antioxidant properties with free radical scavenging activities, which are indirectly able to reduce the inflammatory response and prevent cancer [7,8].

Consuming nutrients rich in anti-inflammatory bioactive components from plants, such as polyphenols and flavonoid compounds with antioxidant activities, has demonstrated anti-inflammatory activity with reduced inflammation in breast cancer tissue [9]. The health benefits of the regional diet are accredited for having a substantial quantity of bioactive compounds recognized as foods containing potential antioxidant and anti-inflammatory activities [10]. There have been several studies on cells, animals, and human clinical trials that can provide substantial proof that bioactive components found in the diet may perform as an anti-inflammatory and antioxidant mediator, especially in elevating energy usage and increasing the thermogenesis of the body while reducing oxidative stress and inflammation [11–14]. The previous literature has suggested that consuming mixed fruits and herbal supplements significantly reduces oxidative stress activity and elevates antioxidant levels in systemic circulation [15,16]. Research laboratory experiments have shown that the anticancer potential of a polyphenol-rich fraction of herbal extracts may be due to the capability of polyphenols to act directly or indirectly on cancer tissues without any side effect on normal cells [17]. The aim of this study was to evaluate the bioactive compounds of essential oil and different extractions of *Mentha longifolia* L., as well as its antioxidant and anticancer activities against the Caco-2 and SW48 cell lines. Additionally, the molecular mechanism and induction of apoptosis in colorectal cancer were assessed.

## 2. Materials and Methods

All the methods used in this study were developed and published previously by our research group, and we performed them with no additional modifications.

### *2.1. Extraction Procedure*

The aerial parts of the *M. longifolia* L. were extracted based on a previously published method [18]. The essential oil was extracted using Soxhlet, as described earlier by Ghareh Bashlouei et al. [19].

### *2.2. Phenolic and Flavonoid Content*

Total phenol (TPC) and flavonoid contents (TFC) of *M. longifolia* L. extracts were determined and extracted based on a previously published method [20].

### *2.3. Method of Gas Chromatography–Mass Spectrophotometry*

The samples were processed based on a previously published method [21]. The analysis of the bioactive compound peak was used based on the National Institute of Standards and Technology (NlST 08 and NIST 08s) library.

### *2.4. FRAP Assay*

The assay was performed based on a published paper [22]. The percentage of antioxidant activity in the FRAP assay of the samples was calculated according to the formula below:

$$\text{Antioxidant Activity (\%)} = (A1 \times A0)/A1$$

A0 = absorbance of the control (potassium phosphate buffer + FRAP reagent) and A1 = absorbance of the sample.

### 2.5. Apoptotic Activity

Apoptotic activity was performed based on a published method [19]. Real-time PCR was applied under the below condition: 95 °C, 15 min 1 cycle (holding step), 95 °C 15 s, 58.5 °C, 20 s 39 cycles (annealing), 72 °C, 20 s 39 cycles (extension); 65–95 °C, 1 cycle (melting). GAPDH was used as a housekeeping gene [19].

### 2.6. Statistical Analysis

Data were analyzed by one-way ANOVA, using the MIXED procedure of the SAS software package, version 9.1 (SAS Inst. Inc., Cary, NC, USA). The data were checked for normality using the UNIVARIATE procedure of SAS software Version 9.4. Differences in a $p$-value of <0.05 were significant.

## 3. Results

### 3.1. Total Phenolic and Flavonoid Analysis

The obtained results from different extractions of *Mentha longifolia* L. revealed that the methanolic extract had the highest TPC and TFC with respective values of 59.25 mg GAE (gallic acid) eq./g DW (dry weight) and 20.02 mg RE eq./g DW, respectively, compared to hexane and diethyl ether. As shown in Table 1, all the extracts were significant ($p < 0.05$).

**Table 1.** Total phenolic and flavonoid compounds of essential oil and extracts of *Mentha longifolia* L.

| Extraction | Phenolic Content [1] | Flavonoid Content [2] |
|---|---|---|
| Hexane | 18.43 ± 2.51 [c] | 9.36 ± 1.16 [c] |
| Methanol | 59.25 ± 4.39 [a] | 26.02 ± 3.13 [a] |
| Diethyl ether | 30.15 ± 3.72 [b] | 14.21 ± 2.55 [b] |

Each value represents the mean of three replicates. [a–c] Means in the same column with different superscripts are significantly different ($p < 0.05$).[1] mg gallic acid equivalents/g DW. [2] mg rutin equivalents/g DW.

### 3.2. Gas Chromatography–Mass Spectrophotometry of Mentha longifolia L. Compounds

The volatile compounds screening was conducted using GCMS analysis in the methanolic extracts and essential oils of *Mentha longifolia* L., which led to various natural components (Tables 2 and 3). Among them, piperitenone oxid and piperitonone were found to be the dominant compounds in methanolic extracts and essential oils.

**Table 2.** Bioactive profiling of *Mentha longifolia* L. essential oil using gas chromatography–mass spectrophotometry.

| Number | Main Compound | Composition (%) |
|---|---|---|
| 1 | Limonene | 6.7 |
| 2 | Pulegone | 12 |
| 3 | Piperitonone | 13.9 |
| 4 | Piperitenone oxid | 21.8 |

**Table 3.** Bioactive profiling of methanolic extract of *Mentha longifolia* L. using gas chromatography–mass spectrophotometry.

| Number | Main Compound | Composition (%) |
|---|---|---|
| 1 | Pulegone | 6.4 |
| 2 | Eucalyptol | 10.9 |
| 3 | Cis-nepetalactones | 14.1 |
| 4 | Piperitonone | 17 |
| 5 | Piperitenone oxid | 18.8 |

### 3.3. Antioxidant Potential

The antioxidant properties of *Mentha longifolia* L. essential oil and different solvent polarity extraction were conducted using FRAP assay. The results showed that (Figure 1) the essential oil and different fractionations exhibited a more potent reduction of $Fe^{3+}$ as free radicals. As shown in Table 4, the methanolic extract was more active compared to other fractionations and essential oils. The free radical scavenging of *Mentha longifolia* L. essential oil, various extractions, and standards at a concentration of 400 µg/mL (Table 4) were found to be in the ascending order: vitamin E > methanol > essential oil> diethyl ether > hexane, respectively.

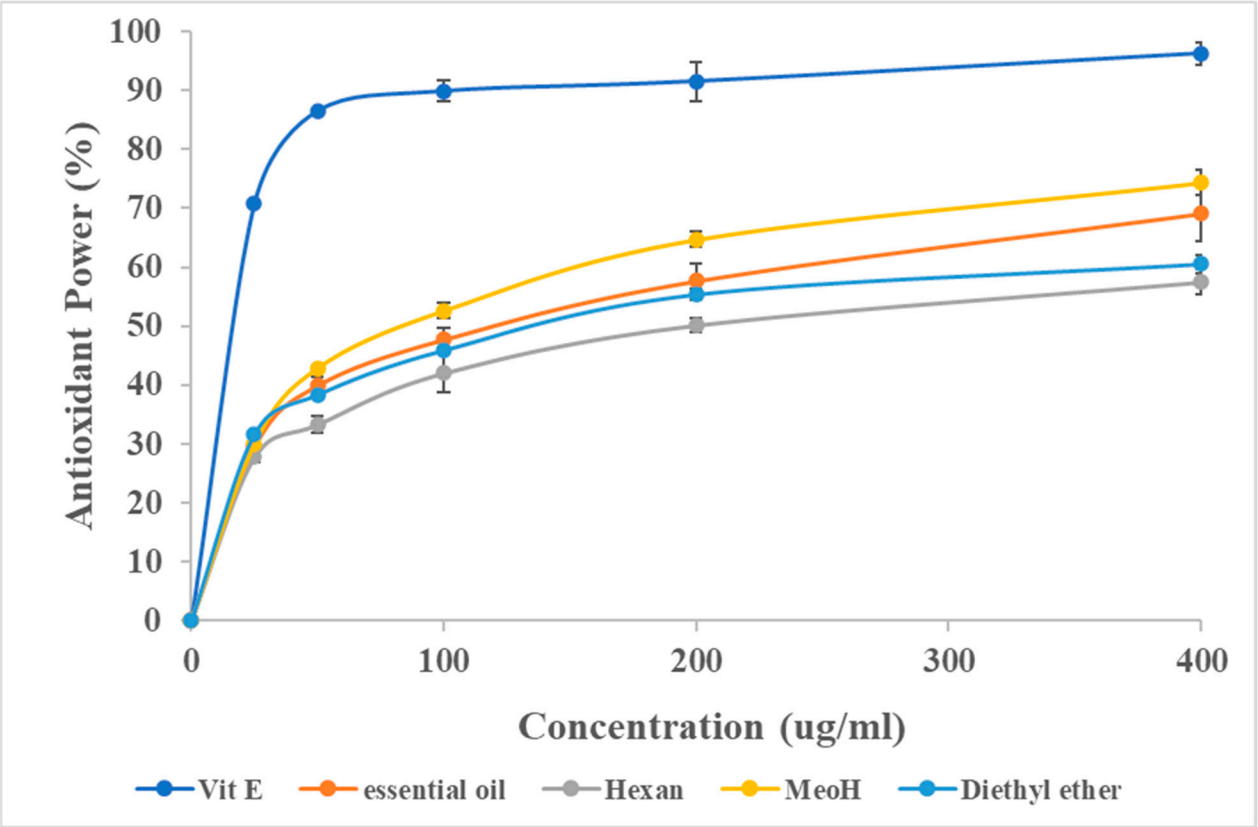



**Figure 1.** The free radical scavenging of *Mentha longifolia* L. essential oil and different fractions.

**Table 4.** FRAP activity of *Mentha longifolia* L. essential oil and extracts using different solvents (hexane, methanol, diethyl ether).

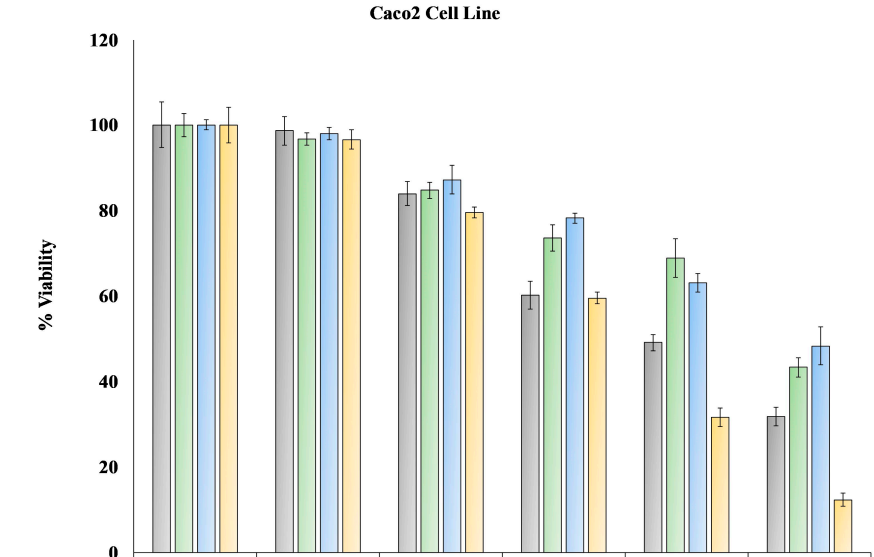
| Extraction | FRAP (400 µg/mL) [2] |
|---|---|
| Essential oil | 69.11 ± 2.09 [c] |
| Hexane | 57.50 ± 3.7 [e] |
| Methanol | 74.36 ± 3.5 [b] |
| Diethyl ether | 60.60 ± 2.8 [d] |
| Vitamin E [1] | 96.23 ± 4.2 [a] |

[1] Vitamin E as positive controls. [2] Analyses: mean of triplicate measurements ± standard deviation. Results expressed in percent of antioxidant power at 400 µg/mL. [a–e] Means not sharing a common letter within a column was significantly different at $p \leq 0.05$.

### 3.4. Anticancer Properties

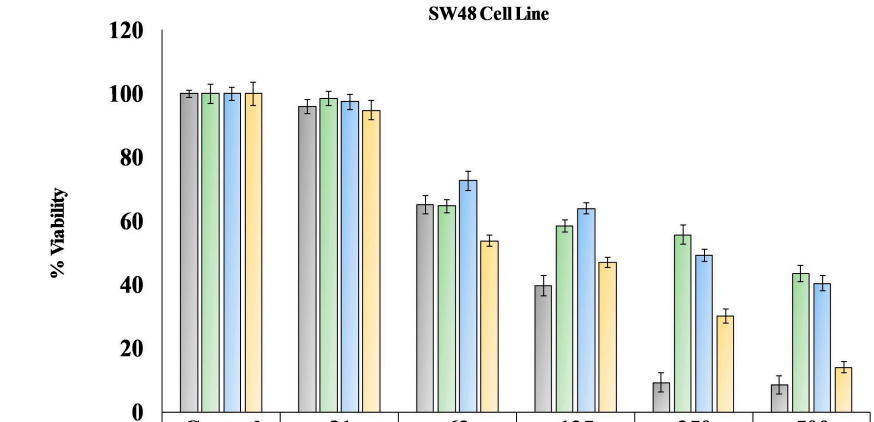
The cytotoxicity assessment of *M. longifolia* L. fractionation against colorectal cancer (Caco-2 and SW48) is presented in Figures 2 and 3. In the light of this experiment, an

increase in various extract concentrations up to 500 µg/mL decreased the cell viabilities notably ($p < 0.001$) in a dose-dependent manner in the mentioned cancer cell line. The anticancer activity of methanolic extract appeared to be more remarkable on the Cac02 ($IC_{50}$ = 167.6) and SW48 (IC50 = 97.3) cell lines compared to other extractions. Doxorubicin was used as a positive control in this study (Table 5). Furthermore, our results illustrated that all the extractions of *M. longifolia* L. exhibited low toxicity against the HFF cell line as a normal cell (Figure 4).




| | Control | 31 | 62 | 125 | 250 | 500 |
|---|---|---|---|---|---|---|
| Essential oil | 100.00 | 98.67 | 83.93 | 60.19 | 49.10 | 31.86 |
| Hexan | 100.00 | 96.77 | 84.71 | 73.57 | 68.87 | 43.34 |
| Diethyl ether | 100.00 | 97.93 | 87.20 | 78.18 | 63.02 | 48.29 |
| MeoH | 100.00 | 96.60 | 79.58 | 59.54 | 31.62 | 12.38 |

**Figure 2.** The impact of *Mentha longifolia* L. essential oil and different fractionations on the viability of the Caco-2 cell line. All values represent the mean ± standard deviation from three independent experiments.



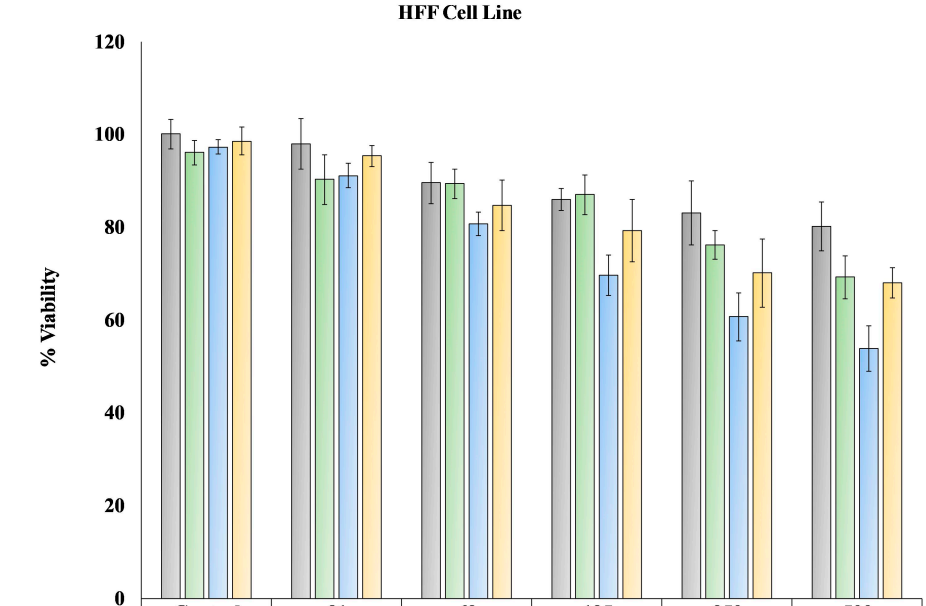

| | Control | 31 | 62 | 125 | 250 | 500 |
|---|---|---|---|---|---|---|
| Essential oil | 100.00 | 96.06 | 65.08 | 39.80 | 9.32 | 8.61 |
| Hexan | 100.00 | 98.52 | 64.77 | 58.44 | 55.74 | 43.58 |
| Diethyl ether | 100.00 | 97.42 | 72.66 | 63.99 | 49.29 | 40.50 |
| MeoH | 100.00 | 94.85 | 53.81 | 47.01 | 30.18 | 14.12 |

**Figure 3.** The impact of *Mentha longifolia* L. essential oil and different fractionations on the viability of SW48 cell line. All values represent the mean ± standard deviation from three independent experiments.

**Table 5.** $IC_{50}$ values of *Mentha longifolia* L. essential oil and different fractionation and positive control on Sw48 and Caco-2 cell lines.

| Extraction | $IC_{50}$ Value (µg $mL^{-1}$) | |
|---|---|---|
| | Caco-2 | SW48 |
| Essential oil | 239.9 [c] | 99.57 [b] |
| Hexane | 434.8 [b] | 368.43 [a] |
| Methanol | 167.6 [d] | 97.33 [b] |
| Diethyl ether | 471.1 [a] | 175 [c] |
| Doxorubicin | 1.826 [e] | 1.11 [d] |

[a–e] Means in the same column with the different superscripts are significantly different at $p < 0.05$. (Mean ± SEM; n = 3)




| | Control | 31 | 62 | 125 | 250 | 500 |
|---|---|---|---|---|---|---|
| Essential oil | 100.00 | 97.88 | 89.47 | 85.90 | 83.06 | 80.12 |
| Hexan | 96.00 | 90.21 | 89.34 | 86.95 | 76.14 | 69.20 |
| Diethyl ether | 97.25 | 91.08 | 80.64 | 69.59 | 60.63 | 53.90 |
| MeoH | 98.50 | 95.28 | 84.66 | 79.26 | 70.06 | 67.97 |

**Figure 4.** The impact of *Mentha longifolia* L. essential oil and different fractionations on the viability of the HFF cell line. All values represent the mean ± standard deviation from three independent experiments.

### *3.5. Flow Cytometry Observation*

According to our previous results, methanolic extraction exhibited the strongest antioxidant and anticancer potential, so further experiments, including flow cytometry and gene expression methanolic extraction, have been selected. The flow cytometry findings showed a significant increase in the SubG1 peak (53.4%) in Caco-2 and SW48 (75%) cell lines by enhancing treatment doses of methanolic extraction of *M. longifolia* L. The results confirmed the apoptotic death in both treated colorectal cancer cell lines of Caco-2 and SW48 (Figure 5).

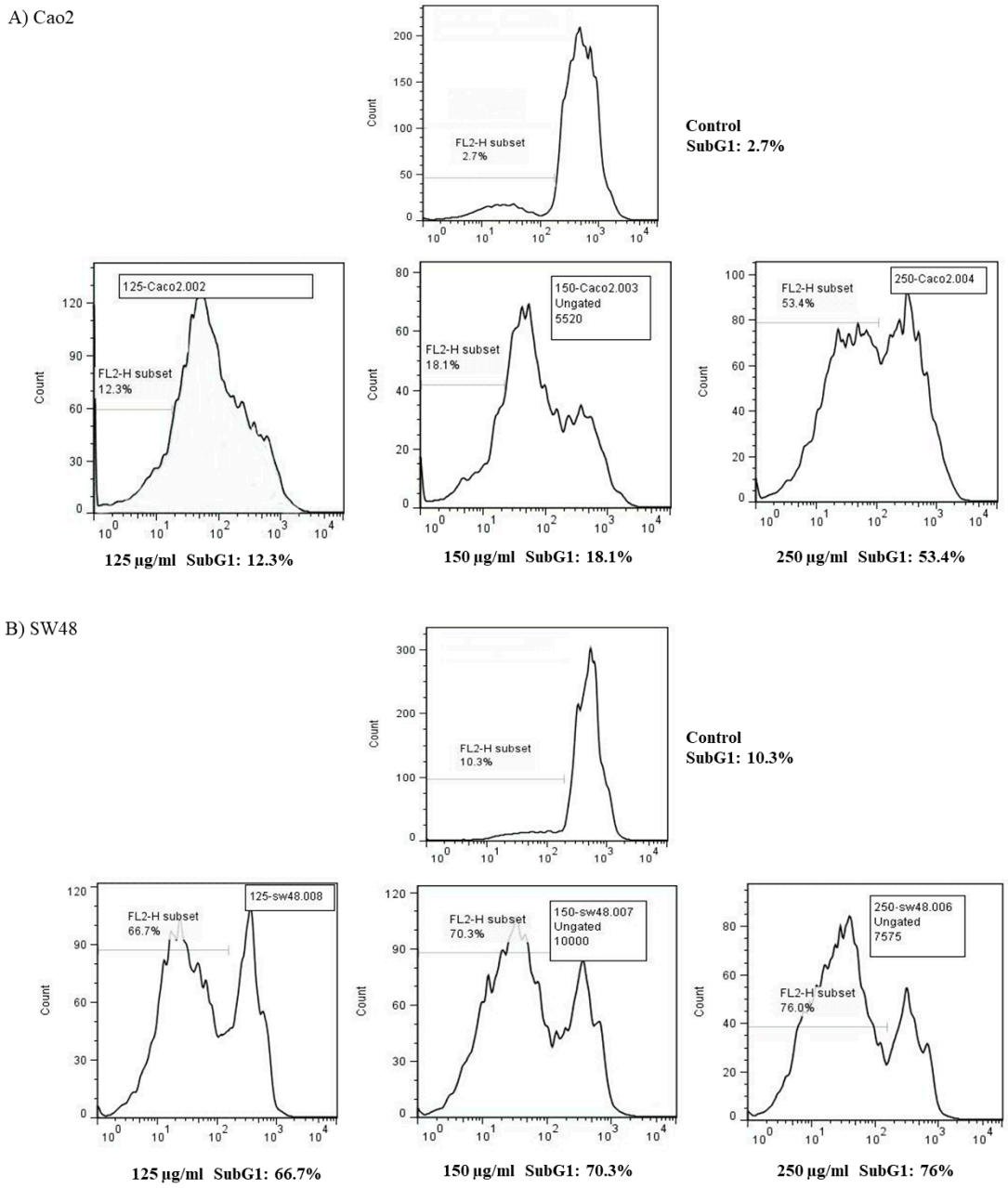



**Figure 5.** Flow cytometric evaluation of the cell cycle in colorectal cancer cell lines (Caco-2 and SW48) treated with methanolic extraction of *M. longifolia* L. Increased in the SubG1 peak in Caco-2 (**A**) and SW48 (**B**) cell lines by enhancing treatment doses of methanolic extraction of *M. longifolia* L.

### *3.6. Caspase 3 Gene Expression in Caco-2 and SW48 Cancer Cells*

The caspase 3 gene expression in Caco-2 and SW48 cell lines was significantly up-regulated after 48 h incubation with an $IC_{50}$ concentration of methanolic extraction of *M. longifolia* L. (Figure 6). Our results proved that methanolic extraction resulted in apoptotic death in both mentioned cancer cell lines by up-regulating the caspase 3 gene.

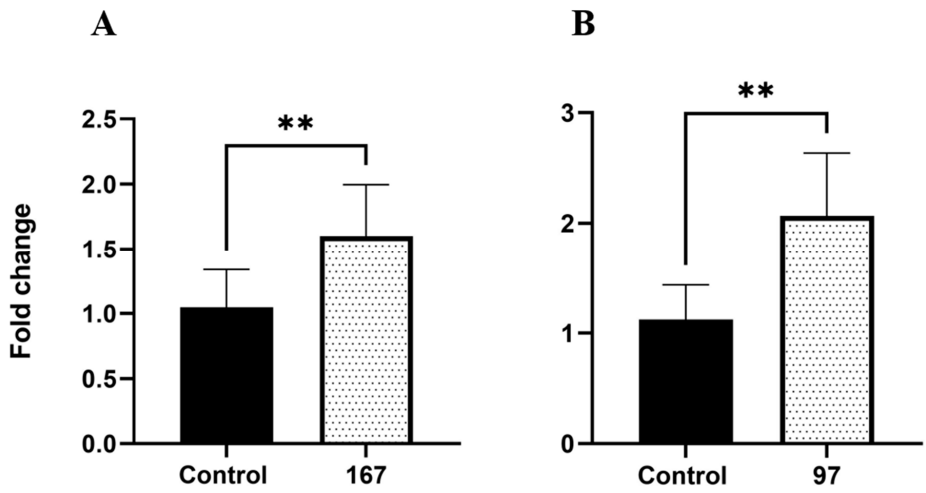



**Figure 6.** Caspase-3 gene profiling in (**A**) Caco-2 and (**B**) SW48 cell lines treated with methanolic extraction of *M. longifolia* L. The ** shows a significant relationship ($p < 0.05$). All values represent the mean ± standard deviation from three independent experiments. Concentrations were µg/mL.

## 4. Discussion

The present study elucidates the mechanism of apoptosis provoked by *M. longifolia* L. extract and its essential oil against colorectal cancer (Caco-2 and SW48). In addition, *M. longifolia* did not reveal any toxic impact on the HFF normal cell line.

Medicinal herbs are commonly used to treat various ailments, including cancer and malignancies [23,24]. Earlier studies showed that natural products could exhibit several biological activities, such as inducing apoptosis-mediated proliferation inhibition through up-regulation of bax and caspase-3 and down-regulation of bcl2 genes [25–27], repressing insulin-like growth factor-1 and inducing Waf-1 gene expression [28,29], glutathione S-transferase activity [30] heat shock protein [31], anti-inflammatory [32,33] and inhibitor of GLI-mediated transcription, a pathway that causes the formation and progression of a variety of tumors [34]. The natural bioactive compound of the Lamiaceae family was also reported to exert anti-proliferative activity, which inhibits oncocyte growth, induction of differentiation, apoptosis, and induces G2/M arrest on cancer cells [35–37], and has potential antioxidant, anti-microbe, and anti-inflammatory properties [38,39]. The data obtained in this research were in agreement with the mentioned experiments. The gene profiling of caspase-3 confirmed the incidence of apoptosis and indicated that the occurrence of apoptosis possibly occurred through the intrinsic mitochondrial pathway. Cell cycle arrest at G2/M has been characterized in detail, in context of DNA damage. These observations enable us to understand the molecular pathways leading to the cellular consequences of cell cycle checkpoint activation. Accordingly, checkpoint activation leads to cell cycle arrest prior to DNA replication (G1/S arrest) or prior to mitosis (G2/M arrest) to allow time for repair. If the damage is irreparable, the cell dies through apoptosis. This phenomenon of apoptosis preceded by metaphasal arrest (G2/M arrest) could be observed in the colon cancer cells treated with M. Longifolia. Overall results obtained from the biological assays suggest that M. Longifolia is a source of bioactive natural phytoconstituents endowed with interesting biological activities, probably mainly as strongly antioxidant and anticancer agents. Thus, the presence of phenolic acids, flavonoids, essential oils and other compounds with possible cytotoxicity and antioxidative action, may present this herbal plant as a new potential source of natural products and a natural antioxidant.

## 5. Conclusions

Based on the results, the methanolic extraction of *Mentha longifolia* L. displays the highest bioactive compounds, appreciable antioxidant, and anticancer power, notably induced apoptosis via caspase 3 gene regulation. Therefore, we recommended that methanolic ex-

traction has the potential to apply to human health and food industries. However, further experiments need to be carried out in animal models.

**Author Contributions:** Conceptualization, E.K.; methodology, N.B. (Nadia Beheshtin), N.B. (Nazanin Beheshtian), H.H.L. and M.S.; software, J.A.; validation, E.K.; formal analysis, E.K.; investigation, N.B. (Nadia Beheshtin), N.B. (Nazanin Beheshtian), J.A.; resources, E.K.; data curation, E.K.; writing—original draft preparation, N.B. (Nadia Beheshtin) and N.B. (Nazanin Beheshtian); writing—review and editing, E.K. and M.S.; supervision, E.K., M.S. and H.H.L. did not analyze the data but provided comments and suggestions based on the analyzed data. All authors have read and agreed to the published version of the manuscript.

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