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# Endometrial Cancer Ameliorating Effect of *Momordica charantia* Extract Through Bitter Taste Receptors

**Keiichi Hiramoto**
Department of Pharmaceutical Sciences,
Suzuka University of Medical Science, 3500–3
Minamitamagaki, Suzuka, Mie 513–8607, Japan

**Hirotaka Oikawa**
Department of Pharmaceutical Sciences,
Suzuka University of Medical Science, 3500–3
Minamitamagaki, Suzuka, Mie 513–8607, Japan

## ABSTRACT

***Momordica charantia* (MC) extract contains various bitter components. These bitter components exert anticancer effects. However, the impact of MC extract on endometrial cancer remains unknown. In this study, we analyzed the effects of the MC extract on endometrial cancer induced by N-methyl-N-nitrosourea (MNU) and estradiol, as well as its relationship with bitter taste receptors. After cancer induction in mice, they were administered MC extract (50 mg/kg) or the bitter receptor antagonist 6-methoxyflavone (6-MOF; 50 mg/kg), three times weekly during the experimental period. The treatment with MC extract alleviated endometrial cancer symptoms, whereas, 6-MOF administration worsened them. MC extract enhanced intrauterine expression of the bitter taste receptor and remained unchanged by the 6-MOF treatment. MC extract treatment increased the abundance of this bitter taste receptor on macrophages and mast cells, whereas, their abundance was elevated in neutrophils after 6-MOF treatment. Furthermore, the cancer-associated increase in the frequency of myofibroblasts was significantly suppressed after MC extract treatment and enhanced by 6-MOF. Our results demonstrate the MC extract-induced alleviation of endometrial cancer, which was aggravated by 6-MOF treatment. We propose the regulation of this phenomenon through a signaling pathway mediated by bitter taste receptors.**

**Keywords:** *Momordica charantia* extract, 6-methoxyflavone, taste receptor type 2 member 1, endometrial cancer, myofibroblasts.

## INTRODUCTION

The bitter taste is perceived by the G protein-coupled receptors (GPCRs) belonging to the taste receptor type 2 (T2R) family [1]. Previously, 25 and 35 T2R subtypes have been reported in humans and mice, respectively, which are involved in receiving many bitter substances [2]. Bitter taste receptors are also present in the tongue, nose, respiratory tract, heart, lungs, brain, pancreas, intestines, and genitals [3–7]. Bitter taste receptors detect bitter substances produced by harmful bacteria, eliminate them via ciliary movement, and release nitric oxide (NO) that exhibits bactericidal and antibacterial effects [8]. Recent studies demonstrated bitter taste receptors expressed on immune cells, such as macrophages, neutrophils, and

lymphocytes. These receptors expressed on lymphocytes control the migration of lymphocytes that infiltrate the skin [9]. Bitter taste receptors expressed on macrophages and neutrophils elevate NO production and acute phagocytosis, however, the details of associated signal transduction remain unclear [10].

*Momordica charantia* (MC), also known as bitter melon, is a plant belonging to the Cucurbitaceae family; it is native to tropical Asia. MC contains large amounts of bitter components, including momordecin, charantan, and cucurbitacin. Momordecin and cucurbitacin protect the gastrointestinal mucosa and stimulate appetite [11], whereas, momordecin and chalantan can reduce blood sugar levels [12]. Recently, MC has been reported to exhibit anti-inflammatory, antibacterial, and antiviral effects [13–15]. Furthermore, the MC extract is also effective against tumors [16]; it suppresses the growth of malignant tumors, including stomach, cancer, and breast cancers [17].

The main types of gynecological cancers include malignancies in the ovary, uterine body, cervix, vagina, and vulva [18]. Between 2012 and 2016, approximately 94,000 women were annually diagnosed with gynecological cancers, among which uterine cancer is the most common type [19].

Uterine cancers are categorized into endometrial and cervical cancers. Endometrial cancer primarily affects the uterine body and endometrium; some of these cases are caused by prolonged exposure to estrogen, whereas, others are unrelated to estrogen. The estrogen-related endometrial cancer is closely associated with various factors, such as nulliparity, late menopause, and obesity. Considering the rising incidence of gynecological cancers, including endometrial cancer, identifying additional drugs is urgently needed for their effective treatment and prevention. In this study, we aimed to investigate the role of the MC extract as a natural preventive and therapeutic compound to manage endometrial cancer using a mouse model of endometrial cancer.

## MATERIALS AND METHODS

### Animals and Experimental Design

Twelve-week-old specific-pathogen-free (SPF) Institute of Cancer Research (ICR) mice were obtained from SLC, Hamamatsu, Shizuoka, Japan. Mice were individually housed in cages under a controlled SPF environment with a 12-h light/dark cycle (lights were turned on at 8:00 AM) at 23 ± 1°C. Food and water were provided ad libitum. Furthermore, they were randomly divided into five groups consisting of six mice each: control, endometrial cancer (treated with N-methyl-N-nitrosourea [MNU] and estradiol only), MNU and estradiol + MC extract-treated, MNU and estradiol + MC extract + 6-methoxyflavone (6-MOF, an antagonist of bitter taste receptors)-treated, and 6-MOF treated groups. The animals underwent laparotomy under general isoflurane anesthesia. A solution of MNU (1 mg/100 g body weight [total volume, 0.1 ml]) was injected into the uterus. The control group received an intrauterine infusion of physiological saline. After this 1 week of MNU treatment, mice were administered 17β-estradiol in the endometrial cancer, MC extract-treated, MC extract + 6-MOF-treated, and 6-MOF-treated groups. Previously, 17β-estradiol was used to treat endometrial cancer [20,21]. In this study, the dorsal skin of MNU-treated mice was subcutaneously implanted with pellets (Innovative

Research of America Inc., Sarasota, FL, USA) continuously releasing 17β-estradiol for 60 days at a dose of 0.18 mg. The pellets were subcutaneously implanted three times during the 30-week study period. The experimental schedule is depicted in Figure 1. This study was approved by the Suzuka University of Medical Sciences Animal Experimentation Ethics Committee (September 25, 2014) and was conducted following the recommendations of the Guide for the Care and Use of Laboratory Animals at Suzuka University of Medical Sciences (Approval No: 34). All surgeries were conducted under isoflurane anesthesia with efforts to minimize animal suffering.

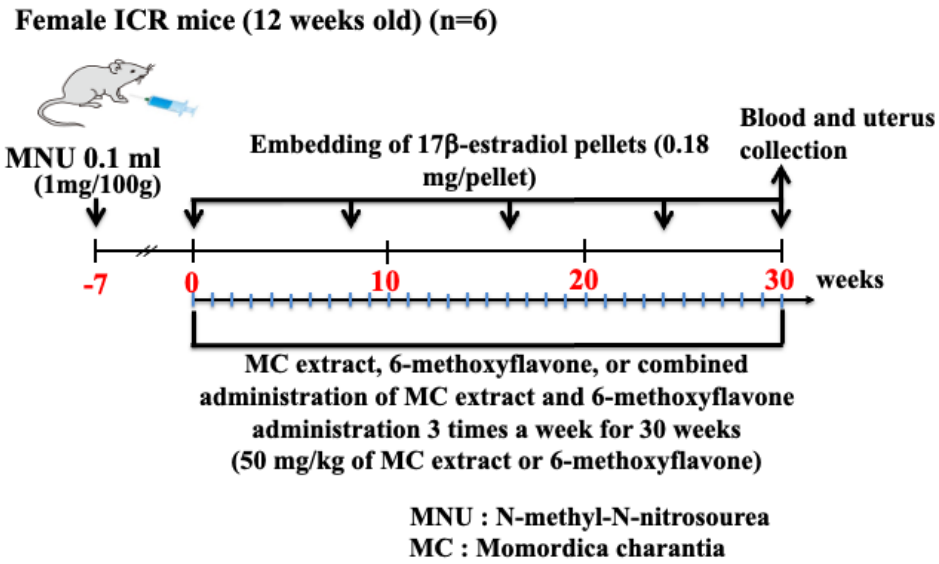



**Figure 1: Schematic presentation of the study procedure**

## MC Extract and 6-methoxyflavone (6-MOF) Treatments

The lyophilized MC was provided by ChromaDex (Irvine, CA, USA). Approximately 20 volumes of 80% (v/v) ethanol were added to the purchased dried MC powder and extracted overnight at 4°C with stirring [22]. The extract (approximately 50 mg/kg body weight) in 0.1% dimethyl sulfoxide (DMSO) was orally injected (p.o.) into each mouse three times per week for 30 weeks. The dosage was determined based on the findings reported by Kobori et al. [22] and Hiramoto and Oikawa [23]. Additionally, the amount of active ingredients in the extracted MC was analyzed (Table 1). 6-methoxyflavone (6-MOF) was kindly provided by INDOFINE Chemical Company, Inc. (Hillsborough, NJ, USA); 6-MOF (approximately 50 mg/kg body weight) in 0.1% DMSO was orally injected (p.o.) in each mouse three times per week for 30 weeks. The solvent-treated control animals were treated with DMSO alone [24,25]. A combination of the MC extract and 6-MOF was orally administered three times a week for 30 weeks.

Table 1. The composition of active ingredience in the MC extracts was determined by high-performance liquid chromatography (Vitamins A and C were measured using commercially kits)

| | Mean value | |
|---|---|---|
| Vicine | 8 mg | (6-10 mg) |
| Momordicin | 30 mg | (22-34 mg) |
| Charntia | 16 mg | (12-18 mg) |
| Momordin | 5 mg | (3-6 mg) |
| Cucurbitacin | 20 mg | (15-26 mg) |
| Alkaloid | 52 mg | (46-60 mg) |
| Flavonoid | 70 mg | (60-75 mg) |
| Vitamin A | 240 mg | (220-260 mg) |
| Vitamin C | 262 mg | (244-284 mg) |

Content in 100 g MC extract

Standard substance for measurement
Vicine: Merk-Aldrich
Momordicin: MedChemExpress
Charantia: ChromaDex Inc.
Momordin: Selleck Co.
Alkaloid: nicotine+morfine+kinine: FUJIFILM Wako
Flavonoid: isoflavone+curcumin+quercetin+catechin+Epigallocatechin: FUJIFILM Wako

## Histological and Immunological Analysis of the Uterus

Uterine samples were collected under anesthesia on the final day of the experiment, fixed using 4% phosphate-buffered paraformaldehyde, embedded in Tissue-Tek O.C.T. Compound (Sakura Finetek, Tokyo, Japan), and cryo-sectioned. Sections were stained using hematoxylin and eosin (HE) for histological analysis of the uterus. The specimens were then stained using antibodies for immunohistological analysis following a previously described protocol [26]. For this analysis, uterus specimens were incubated with rabbit polyclonal anti-taste receptor type 2 member 1 (T2R1) (1:100; Bioworld Technology, Inc., St. Louis Park, MN, USA), rabbit polyclonal anti-placental growth factor (PLGF1; 1:100; Abcam, Cambridge, MA, USA), mouse monoclonal anti-lymphocyte antigen 6 complex locus G6D (Ly6G: marker of neutrophil) (1:100; BD Biosciences, Franklin Lakes, NJ, USA), rat monoclonal anti-F4/80 (marker of macrophage) (1:100; Novus Biologicals, LLC., Centennial, CO, USA), goat polyclonal anti-mast cell tryptase (marker of mast cell) (1:100; Santa Cruz Biotechnology, Santa Cruz, CA, USA), rabbit polyclonal anti-α-smooth muscle actin (α-SMA; marker of myofibroblast) (1:100; Cell Signaling Technology, Inc., Danvers, MA, USA), or rabbit polyclonal anti-vimentin (marker of myofibroblast) (1:100; Cell Signaling Technology, Inc.) primary antibodies. Subsequently, the sections were incubated with fluorescein isothiocyanate-conjugated anti-goat or anti-mouse antibodies, and tetramethylrhodamine isothiocyanate-conjugated anti-rabbit secondary antibodies (1:30; Daco Cytomation, Glostrup, Denmark). Intensities of T2R1, PLGF1, Ly6G, F4/80, mast cell tryptase, a-SMA, and vimentin were estimated based on six random visual fields with constant area using ImageJ software v.1.53 (National Institutes of Health, Bethesda, MD, USA); the original files were converted to monochrome 8-bit files followed by the establishment of a luminous intensity threshold and the measurement of areas exhibiting luminous intensity above the threshold in each sample. These areas were referred to as "intensity."

## Analyses of Carbohydrate Antigen 125, Angiopoietin-Like Protein 2, Tumor Necrosis Factor-α, Interleukin-6, Basic Fibroblast Growth Factor, And Matrix Metalloproteinase-9 Levels in The Plasma

Blood samples were collected from the hearts of the mice on the final day of the experiment. The plasma levels of carbohydrate antigen 125 (CA125), angiopoietin-like protein 2 (ANGPTL2), tumor necrosis factor (TNF-α), interleukin (IL)-6, basic fibroblast growth factor (bFGF), and matrix metalloproteinase (MMP)-9 were determined using commercial ELISA kits (CA125: Bioassay Technology Laboratory, Shanghai, China; ANGPTL2: biorbyt, Cambridge, UK; TNF-α: R&D Systems, Minneapolis, MN, USA; IL-6 and MMP-9: Proteintech, Rosemont, IL, USA; bFGF: Merck, Darmstadt, Germany) following the instructions provided by the manufacturer. The optical density was measured using a microplate reader (Molecular Devices, Sunnyvale, CA, USA).

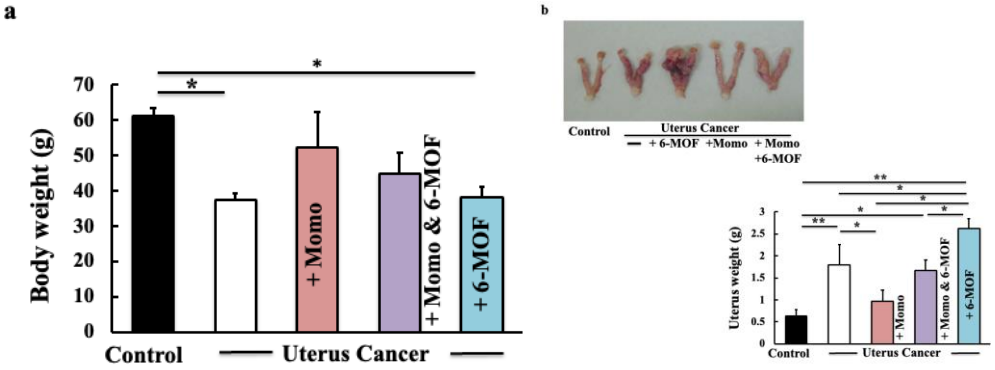
### Statistical Analysis

All data are presented as mean ± standard deviation (SD). Microsoft Excel 2010. (Microsoft Corp., Redmond, WA, USA) was used to analyze the statistical significance of the data, along with a one-way analysis of variance, followed by Tukey's post-hoc test using SPSS v.20 (SPSS Inc., Chicago, IL, USA). Results with *p*-values < 0.05 and 0.01 were considered statistically significant.

## RESULTS

### Effect of MC Extract and 6-MOF on Endometrial Cancer

After the MC extract and 6-MOF treatments, on the final day of the experiment, microscopic analyses of endometrial cancer samples and CA125, a marker of endometrial cancer, revealed alleviated endometrial cancer symptoms in the MC extract-treated group than in the endometrial cancer group (Figure 2a-d). Additionally, the endometrial cancer symptoms worsened in the group treated with 6-MOF (Figure 2a-d). Contrastingly, the MC extract + 6-MOF treatment showed no variations when compared with the endometrial cancer group (Figure 2a-d).



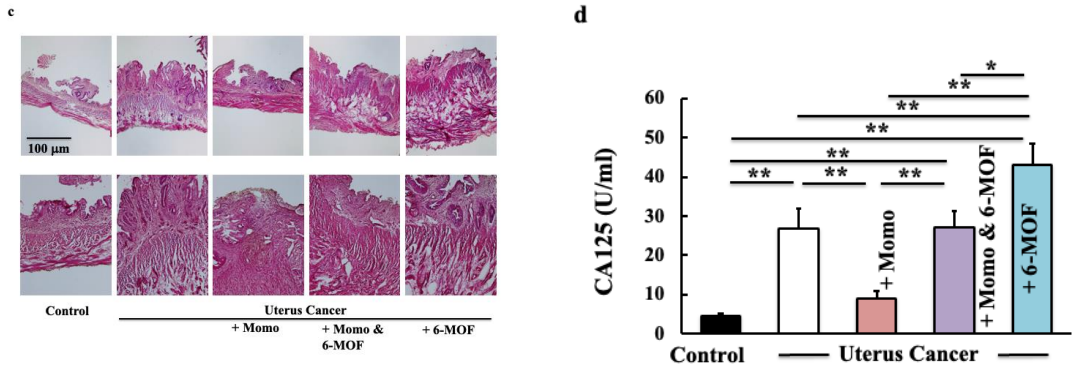



**Figure 2: Effects of *Momordica charantia* (MC) extract and 6-methoxyflavone (6-MOF) treatments on endometrial cancer induced by MNU and estradiol. The variation in the body weight (a), the uterus (b, c), and plasma levels of CA125, a marker of endometrial cancer (d), were measured after the 30-week study period. Data derived from six animals are expressed as mean ± SD. *$p < 0.05$, **$p < 0.01$. Scale bar = 100 μm.**

## Effect of MC Extract and 6-MOF on ANGPTL2, IL-6, and TNF-α Levels in the Plasma

IL-6 and TNF-α levels increased in the endometrial cancer group. However, MC extract treatment reduced IL-6 and TNF-α levels. IL-6 and TNF-α peaked in the 6-MOF-treated group. However, the combination treatment group did not differ from the endometrial cancer group. ANGPTL2 level was significantly increased only in the 6-MOF-treated group (Figure 3a-c).

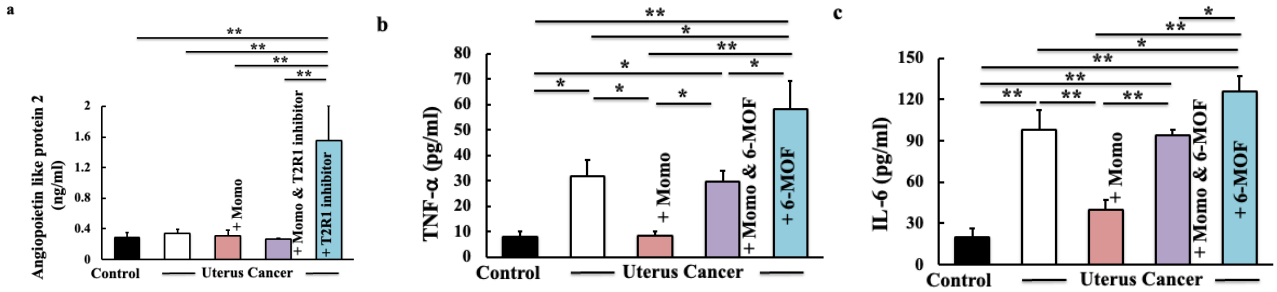



**Figure 3: Effects of MC extract and 6-MOF treatments on the levels of angiopoietin-like protein 2 (ANGPTL2), TNF-α, and IL-6. The ANGPTL2 (a), TNF-α (b), and IL-6 (c) levels in the plasma were measured after the 30-week study using mouse models of MNU- and estradiol-induced endometrial cancer. Data derived from six animals are expressed as mean ± SD. *$p < 0.05$, **$p < 0.01$.**

## Effect of MC Extract and 6-MOF on the Intrauterine Expressions of T2R1, Ly6G, F4/80, and Mast Cell Tryptase

T2R1 expression was markedly increased in the MC extract-treated group than in the endometrial cancer group (Figure 4a). We examined the expression of T2R1 by double-staining cells for T2R1 with Ly6G (Figure 4b), F4/80 (Figure 4c), and mast cell tryptase (Figure 4d). In neutrophils (detected using Ly6G), T2R1 was highly expressed in the 6-MOF-treated group, whereas, T2R1 expression was significantly increased in macrophages (detected using F4/80) and mast cells (detected using mast cell tryptase) of the MC extract-treated group compared to that recorded in the control cells.

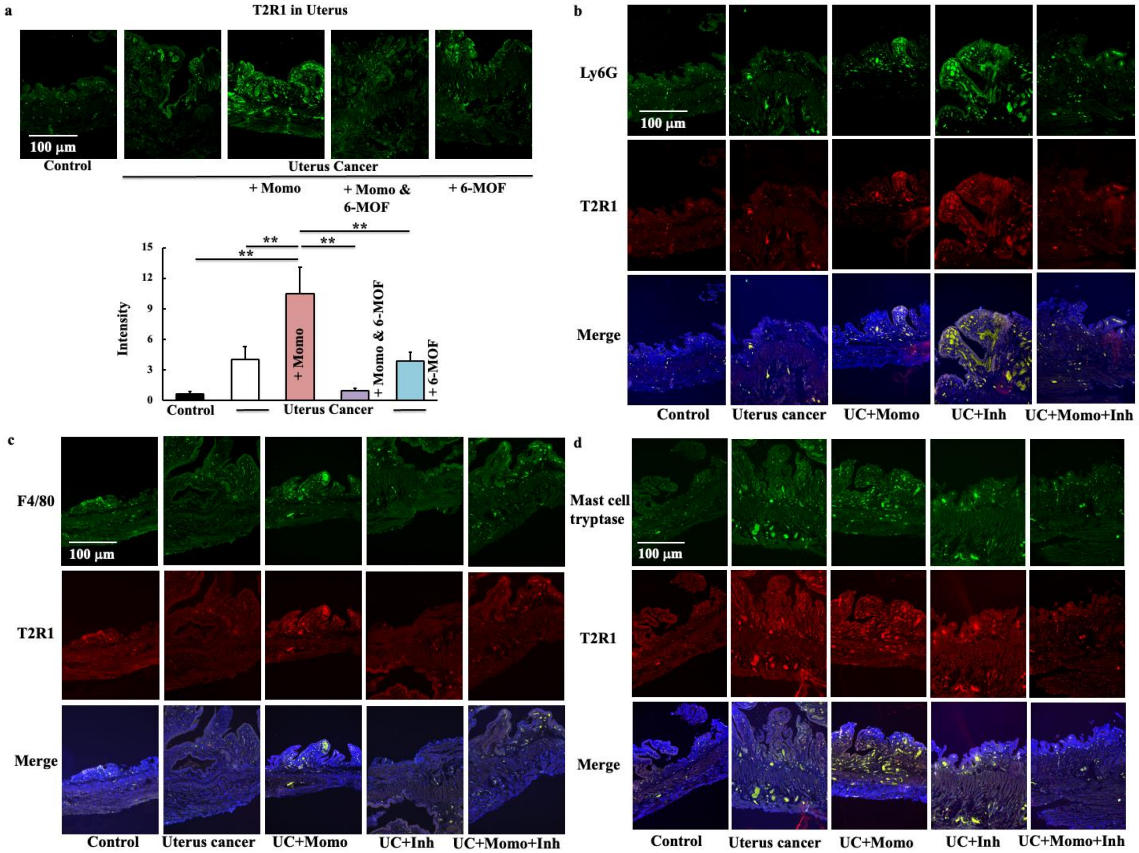
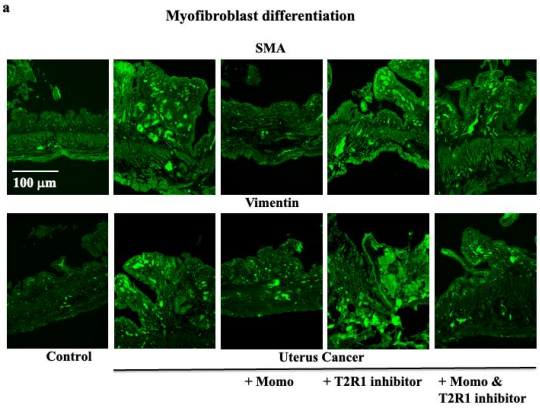



**Figure 4: Effects of MC extract and 6-MOF treatments on T2R1 expression. Variations in the T2R1 expression (a). The colocalization of T2R1 with Ly6G (a marker of neutrophils) (b), F4/80 (a marker of macrophages) (c), and mast cell tryptase (a marker of mast cells) (d). Data derived from six animals are expressed as mean ± SD. Scale bar = 100 µm. Intensity was calculated using five random visual fields with a constant area using ImageJ software. ** $p < 0.01$; * $p < 0.05$.**

## Effect of MC Extract and 6-MOF on the Intrauterine Expressions of SMA and Vimentin

We investigated the expression of the myofibroblast markers, SMA and vimentin, in the uterus. SMA and vimentin levels increased in the uterine cancer group than in the control group and decreased after MC extract treatment. Contrastingly, the 6-MOF-treated group showed the most significant increase in SMA and vimentin compared to the control group (Figure 5a-c).



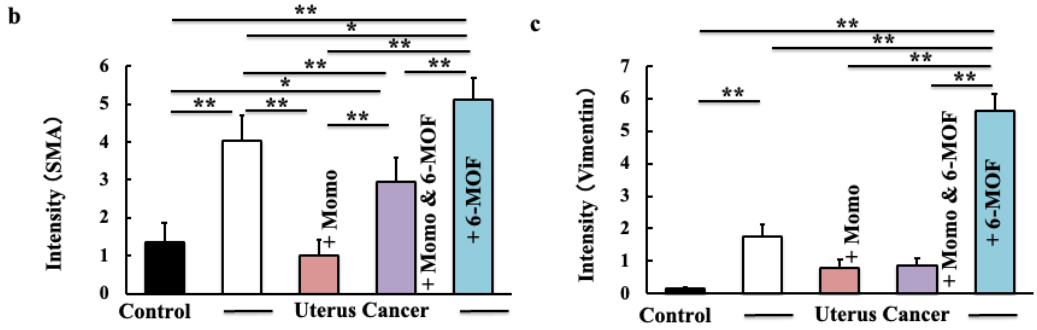



**Figure 5: Effects of MC extract and 6-MOF treatments on the expression of SMA (ANGPTL2) and vimentin. The levels of SMA (a, c) and vimentin (a, c) (myofibroblast markers) in the uteri of the MNU- and estradiol-induced mouse models of endometrial cancer were measured after the 30-week study period. Data derived from six animals are expressed as mean ± SD. Scale bar = 100 µm. Intensity was calculated using five random visual fields with a constant area using ImageJ software. ** $p < 0.01$; * $p < 0.05$.**

## Effect of MC extract and 6-MOF on the expressions of PLGF in urea, and the plasma levels of bFGF and MMP-9

The analyses of PLGF, bFGF, and MMP-9 secreted by myofibroblasts revealed the upregulation of these factors in the endometrial cancer group compared to those in the control group, which was further suppressed by the MC extract. However, in the 6-MOF-treated group, the highest levels of bFGF and MMP-9 were detected (Figure 6a-c).

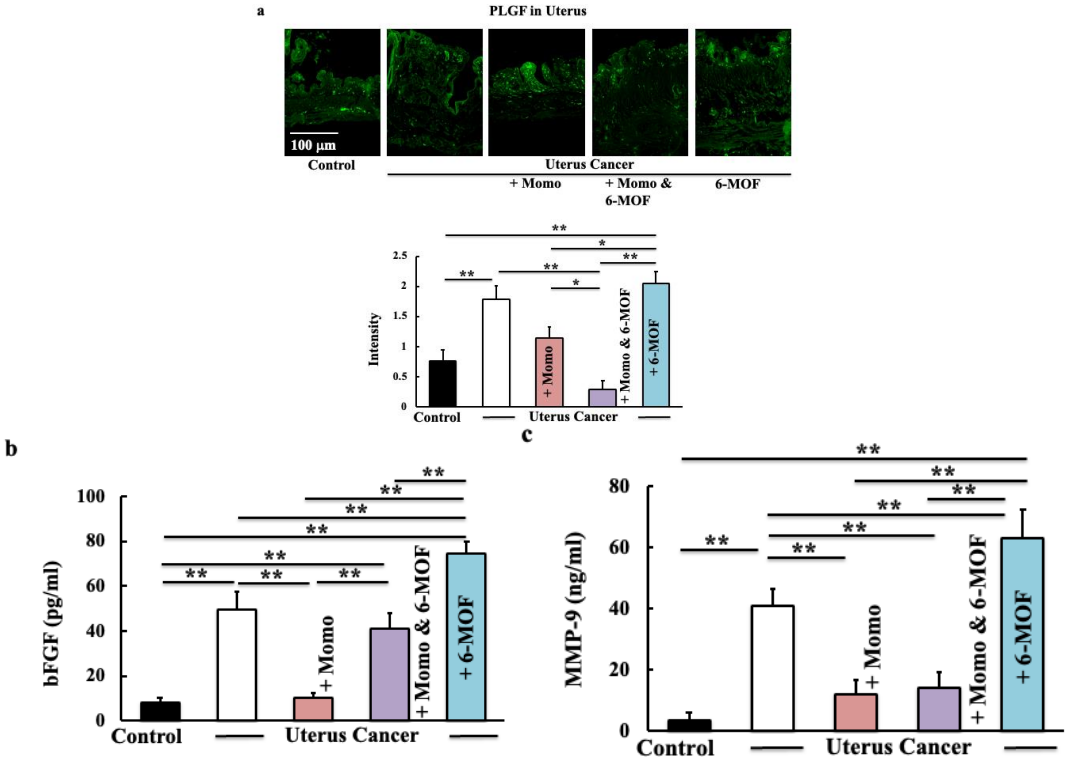



**Figure 6: Effects of MC extract and 6-MOF treatments on the expression of PLGF and the levels of bFGF and MMP-9. The expression of PLGF (a), and the levels of bFGF (b) and MMP-9 (c) in**

**mouse models of MNU- and estradiol-induced endometrial cancer were measured after the 30-week study period. Values are expressed as mean ± SD derived from 6 animals. Scale bar = 100 µm. Intensity was calculated using six random visual fields with constant area using ImageJ software. *$p < 0.05$, **$p < 0.01$.**

## DISCUSSION

In this study, we demonstrated that MC extract treatment reduces the carcinogenic effects of MNU and estradiol using mouse models of endometrial cancer. Furthermore, the administration of 6-MOF, a bitter taste receptor antagonist, significantly worsened endometrial cancer and negated the anticancer effect of MC extract when administered as a combination. Similarly, MC extract suppressed the levels of inflammatory cytokines, including PGATL2, IL-6, and TNF-α, in blood and the abundance of myofibroblasts in the uterus, which were increased in the endometrial cancer group [27,28]. Furthermore, the effect of the MC extract was negated by the combined administration of the MC extract and 6-MOF. Moreover, bitter taste receptors were co-expressed with neutrophils, macrophages, and mast cells and were upregulated after administration of the MC extract.

PGATL2, IL-6, and TNF-α are secreted by M2 macrophages. Moreover, bitter taste receptors are expressed on macrophages [9,10]. Considering the MC extract-mediated increase in the number of bitter taste receptors on macrophages (Figure 4c), we suggest that the bitter components (momovitellin and chlorobitacin) of the MC extract may bind to this bitter taste receptor, thereby suppressing the secretion of inflammatory cytokines by macrophages. This hypothesis is supported by the fact that the bitter taste receptor antagonist resumed and further increased the secretion of inflammatory cytokines, and when it was co-administered with MC extract, these inflammatory cytokines nullified the beneficial anti-cancer effects of the MC extract. Comparably, the MC extract increased the frequency of bitter taste receptors in mast cells, which potentially suppressed the secretion of inflammatory cytokines in these cells (Figure 4d). However, in neutrophils, bitter receptor antagonists possibly increased the number of bitter taste receptors expressed on neutrophils and activate neutrophil migration [9], leading to worsened cancer symptoms (Figure 4b). However, the specific signal transduction pathway stimulated by the interaction between the bitter components of the MC extract and bitter taste receptors expressed on macrophages, neutrophils, and mouse cells remains unknown. Furthermore, although T2R1 was used in this study, the functions of other bitter taste receptors belonging to several subfamilies have not been identified; hence, further research is required to elucidate many unknown aspects of bitter taste receptors and immune cells.

Various interstitial cells involved in cancer include vascular endothelial cells, fibroblasts, myofibroblasts, lymphocytes, and macrophages. Angiogenesis in cancer is regulated by pro-angiogenic factors (vascular endothelial growth factor [VEGF]) and fibroblast growth factor (FGF). Vascular endothelial cells as well as fibroblasts, lymphocytes, and macrophages are involved in promoting angiogenesis, proliferation, and progression of cancer cells [29–32]. In particular, myofibroblasts produce numerous cytokines and chemokines involved in angiogenesis and cell proliferation, including VEGF, FGF, and transforming growth factor-β (TGF-β), as well as proteolytic enzymes, including matrix proteases [33,34]. These comprise a part of the wound-healing program, however, they work to the advantage of cancer cells. In this

study, we detected the upregulation of bFGF, PDGF, and MMP-9 levels [35] in endometrial cancer and that an increased frequency of myofibroblasts worsens cancer. Contrastingly, the levels of myofibroblast/bFGF, PDGF, and MMP-9 were decreased after administration of the MC extract and increased by the treatment with the inhibitor of bitter taste receptor, which suggests the inhibited signal transmission from myofibroblasts via the binding of the MC extract to bitter taste receptors (Figure 7). Our results elucidate a new correlation between myofibroblasts and bitter taste receptors in endometrial cancer, which can potentially lead to the discovery of new molecular mechanisms and the development of new therapeutic strategies for endometrial cancer.

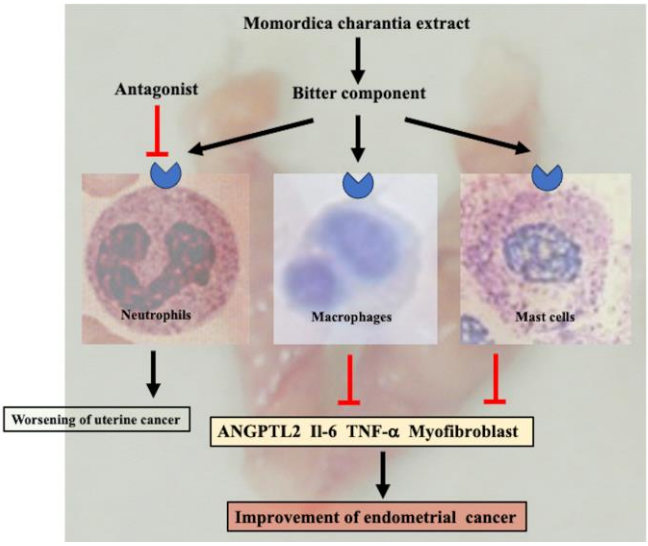



**Figure 7: Mechanism underlying the alleviation of cervical cancer mediated by MC extract.**

**Author Contributions:** K.H. and H.O. performed the experiments and analyzed the data; K.H. and H.O. provided tools and reagents; H.O. conceived and supervised the study; and K.H. designed the experiments and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** All experimental procedures described in the present study were conducted following the Guide for the Care and Use of Laboratory Animals of the Suzuka University of Medical Science (Approval number: 34). All surgeries were performed under pentobarbital anesthesia, and efforts were made to minimize animal suffering.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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