JMM
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.2017.23.3.146
Journal of Menopausal Medicine 2017;23:146-155

Review Article

The Clinical Effects of *Dendropanax Morbifera* on Postmenopausal Symptoms: Review Article

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Postmenopausal women aged 50s generally experience gradual changes in body such as decline in antioxidant and estrogen levels as the body ages. To overcome these aging-associated changes, the needs for health functional foods are increasing. *Dendropanax morbifera* (DM) have antioxidant effects, anti-inflammatory against cancer cells, antidiabetic, and antiatherogenic effect which are associated with postmenopausal symptoms. We analyzed clinical effects of DM on aging-related symptoms by reporting their antioxidant, anticancer and inflammatory activity, etc. and their bioactivity. Data sources EMBASE, SCOPUS, PubMed, Web of Science, and Google Scholar databases were searched up to August 2016 for studies investigating medicinal plants in prevention and treatment of diabetes. The search terms were "*Dendropanax morbifera*". The reference lists of articles were also reviewed for additional relevant studies. Extracts of DM have various efficacy such as antioxidant, anti-cancer, anti-inflammatory activity and anti-thrombotic effect. **(J Menopausal Med 2017;23:146-155)**

Key Words: Aging · Antioxidants · Dendropanax morbifera · Menopause · Plant extracts

Introduction

The needs for health functional foods are continuously increasing, and many efforts are made for the development of health functional foods from natural materials. Extracts from red ginseng, fructus sophorae, pomegranate are representative health functional foods in Korea along with aloe, omega-3, glucosamine, especially in postmenopausal women aged 50s.[1] As the body ages, women are likely to suffer from heart disease, breast cancer, osteoporosis, depression, and autoimmune disease due to many reasons including aging, sex hormone unbalance, etc.[2] Elderly women aged ≥65 years account for over 20% of the Korean population.[3] Aging-associated symptoms such as sarcopenia, increased-body fat, decrease in bone mineral density are generally seen in postmenopausal women, due to their reduced ovarian function and estrogen levels.[4]

Medicinal plants have played significant roles such as curing various disease and maintaining the health. *Dendropanax morbifera* (DM)[5] is classified as a subtropical evergreen, distributed in Malay Peninsula, Latin America and Southeast Asia, etc. (Table 1). Above all, DM of South Korea is known to distributed in throughout the southern regions of Korea. Dendro means "tree", panax means: "panacea" which means panacea trees. This plant including leaf, stem, and root has been traditionally used as an oriental medical plant for various disease such as infectious diseases, skin, dysmenorrhea and migraine.[6] DM extracts positively affects

Received: August 22, 2017 **Revised:** October 11, 2017 **Accepted:** October 16, 2017
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Table 1. In vivo study lists

References	Active part of DM	Patient (animal model)		Outcome	
		N	Age	Outcome measure	Main outcome
Seo et al.[5]	Fresh leaves, ethanolic extract	61 (not meeting inclusion criteria, n = 1)	23–65 years	Serum Cd level, Hg level, MDA level, SOD1 activity	Increased in serum Cd levels (P = 0.3008). Decreased in Serum Hg levels decreased in two groups, but decreased in the DML-male and DML-female groups compared to the placebo-male and placebo-female groups, respectively (P = 0.1336 and P = 0.1937, respectively). Serum MDA levels were increased in the DML-male group compared to the placebo-male group (P = 0.3125). SOD1 activity is increased in DM-female group compared to the placebo-female (P = 0.02031). No significant difference in SOD1 activity was observed between the placebo-male and DML-male group (P = 0.2031).
Kim et al.[13]	Leaf, distilled and deionized water	21	4 weeks	Hg levels, ROS formation and lipid peroxidation, SOD1, CAT, GPx activities, hippocampal level of TSH and activities of GST and GR	Hg concentration was significantly decreased to 75.4% of that observed in the MeHg group (P < 0.05). In the DML-MeHg group, the DCF fluorescence intensity and MDA levels were significantly decreased (P < 0.05). SOD1 and GPx activities were significantly increased to 94.9% and 93.8% of the control values, respectively (P < 0.05). CAT activity only showed a slight increase, compared with the control group, and this change was not statistically significant. The TSH level was slightly increased compared with that in the MeHg group, while GST activity was decreased (not statistically significant). GR activity in the DML-MeHg group was significantly increased to 148.8% of the value in the MeHg group (P < 0.05).
Kim et al.[14]	Stem, 80% ethanol	29	7-week-old rat	Cd level, ROS, lipid peroxidation, protein carbonyl levels, antioxidant activity, glutathione-related enzymes	Cd concentrations in serum, kidney and hippocampal tissues were similar in the control and DMS-treated groups. Serum and kidney Cd concentrations in the Cd-treated group were significantly higher than those in the control group. In the Cd-DMS treated group, the Cd concentrations in the serum and kidney were significantly lower than those in the Cd-treated group. DCF fluorescence was significantly increased in the Cd-treated group compared to the control group (1.71-fold). However, MDA levels in the Cd-DMS-treated group were 74.4%. The protein carbonyl concentration in the Cd-DMS-treated group was 57.4% of the protein carbonyl concentration in the Cd. The levels of MDA in the hippocampal homogenate were 25.8 nmol/mg protein and 25.4 nmol protein in the control and DMS-treated groups, respectively. The levels of MDA in the Cd treated group were 2.2 times higher than those in the control group. However, MDA levels in the Cd-DMS-treated group were significantly lower than those in the Cd-treated group (39.1 nmol/mg protein). SOD1 and GPx activities were slightly higher in the DMS group than in the control group. However, CAT activity was lower than that of the control group. The SOD1, CAT and GPx activities of the Cd-DMS treated group were significantly higher than those of the Cd treated group and the GPx activity was the highest. The TSH concentration and GR activity in the Cd-DMS-treated group were significantly increased to 172.9% and 174.7%, respectively, in the control group. The GST activity of the Cd-DMS-treated group was 58.5%.

Table 1. Continued

References	Active part of DM	Patient (animal model)		Outcome	
		N	Age	Outcome measure	Main outcome
Oka and Saito[18]	Leaf, methanolic extract	1	A 37-year-old woman	Patch testing	She also showed a positive response to the leaves of Fatsia japonica in the patch test because she also had a comp of Fatsia japonica. She also responded positively to Hedera helix and Schefflera arboricola. There is a mutual reaction between Dendropanax trifidus, Fatsia japonica, Hedera helix, and Schefflera arboricola, all of which belong to the Araliaceae family.
Oka et al.[19]	Leaf, 80% methanolic extract	Subject: 2, control subject: 18	A 75-year-old man, a 43-year old woman	Allergenicity, cross-reactivity	A total of 18 normal controls were subjected to a patch test with the leaves of Dendropanax trifidus. The results were as follows: 4 animals were diluted 0.05% and the activity of Dendropanax trifidus and Cis-9, 17-octadecadiene-12, 14-diyne-1, and 16-I looked. The results suggest that this is the major allergen of Dendropanax trifidus.
Choi et al.[20]	Leaf, 80% ethanolic extract	-	Approximately 4–6 weeks old	Rutin	Rutin inhibited blood clot formation. U-PA suppressed blood clot formation by 85% at 50 IU. Rutin caused the inhibition of blood clot formation by 60% at 50 mg (0.27 mM).

DM: *Dendropanax morbifera*, Cd: cadmium, MDA: malondialdehyde, SOD1: superoxide dismutase 1, ROS: reactive oxygen species, CAT: catalase, GPx: glutathione peroxidase, TSH: thyroid-stimulating hormone, GST: glutathione S-transferase, GR: glutathione reductase, DML: *Dendropanax morbifera Léveille*, MeHg: methylmercury, DCF: dichlorofluorescein, DMS: dimethyl sulfate, U-PA: urokinase-plasminogen activator

postmenopausal and aging related symptoms by having antioxidant effects,[7] anti-inflammatory against cancer cells,[8] antidiabetic effect through *in vivo* experiments[9] and antiatherogenic activity.[10] A polyacetylene compound isolated from DM leaves has shown anticomplementary activity,[11] methanol extracts of leaves, stem and branches of DM discover antioxidant activity by analyzing in vitro study.[7]

In this review, we have analyzed clinical effects of Korean traditional plants DM. To the best of our knowledge, no review paper of DM has investigated the clinical effects of DM extracts. The purpose of this paper is to report various effects of DM extracts (e.g., antioxidant activity, anticancer and inflammatory activity, etc.) and their bioactivity.

Study Selection

The data sources EMBASE, Scopus, PubMed, Web of Science, and Google Scholar databases were searched up to August 2016 for studies investigating medicinal plants in prevention and treatment of diabetes. The search terms were "*Dendropanax morbifera*". The reference lists of articles were also reviewed for additional relevant studies. Duplicate studies and out-of-subject research studies were excluded from this study and a total of 21 paper was selected (Fig. 1).

What's in a DM?

Araliaceae is a branch of the *Archichlamydeae* plants. There are more than 1,300 species in 50 genera distrib-

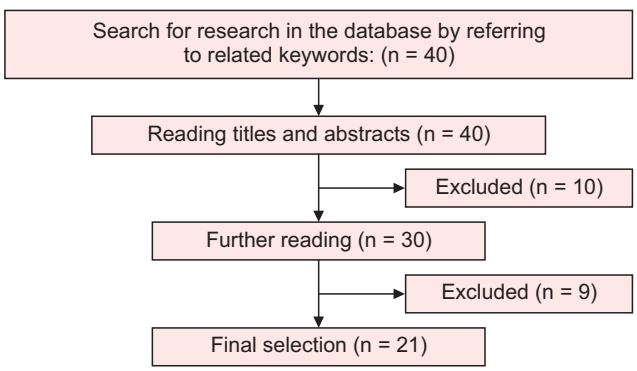

Fig. 1. Search and selection of published articles.

uted throughout the world. Fifteen species of 9 genera are distributed in Korea, including *Acanthopanax sessiliflorus*, *Kalopanax pictus* and DM etc. Among them, DM is traditional medicinal plants found in South Korea and is mainly distributed in the Jeju Island, and near of the Korea coastline (Table 2).[12]

DM's Korea name derives from the name Hwangchil, because it was used to vanish at lacquer color the woodwork surface. It has been used as the finest traditional paint since the *Baekje* period, and it was an export item that has been exported to royal furniture and building materials such as Japan and China. DM has a unique aroma that shows the calming and stabilizing effect of benzoic acid in the physiological activity. After painting, the fragrance lasts more than two years, and it is known that it absorbs ultraviolet rays and electromagnetic waves. The use of this yellowtail has continued until the *Joseon Dynasty*, but it has been cut off due to the lack of understanding of the amount of yellowtail in the late *Joseon Dynasty*, the depletion of harvested tree resources and the decline of refining technology.

DM is 15 meters high, the young branches are green and have no hairs. The leaves are divided into three branches, but after a while they spread all over one another, and the flowers bloom in light yellow-green color from June to the middle of August. The resin of the tree used for the DM is collected from August to September.

DM has been used as medicinal tea and medicine traditionally. DM has a variety of effects, such as dysmenorrhea, migraine headache and rheumatic arthritis. Such efficacy has sufficient value as functional material and food. Postmenopausal women experiencing hormonal changes and aging are vulnerable to various inflammations and diseases including osteoporosis, diabetes, etc. DM is expected to be applicable to these aging and postmenopausal-related diseases due to their antioxidant effects, anti-inflammatory against cancer cells, anti-diabetic effect, and anti-atherogenic activity.

Antioxidant Activity

Generally, decline in estrogen levels during postmenopausal period increases levels of oxidative stress. The antioxidant activity of estrogen is lost after the onset of menopause. Antioxidant is a term for substances that prevent oxidation, and it is known that active oxygen is involved in various diseases. Several substances with antioxidant properties are contained in various natural products. Especially medicinal plant is used as traditional sources of natural antioxidants. Although DM has various effects, studies on antioxidant capacity are the most known.

According to the only clinical trial paper on DM,[5] the effects of DM extract on cadmium (Cd) and mercury secretion and oxidative activity were studied in a randomized, double-blind placebo-controlled clinical trial. A total of 60 patients were divided into 30 test groups and 30 comparative control groups. The placebo group was similar in all respects to the test group, with no restrictions on food and water intake. DM extract group significantly increased Cu, Zn-superoxide dismutase (SOD1) activity compared to the placebo group (P = 0.020). And malondialdehyde (MDA) levels as an oxidative stress and antioxidant marker measured. MDA level is increased in the DM-male group compare with placebo male group (P = 0.312). Also, there was no significant difference in DM Léveille (DML)-females compared to placebo-females (P = 0.084). Activity of serum SOD1 was increased in DML group. Compared to placebo group, SOD1 activity was significantly increased in DML group (P = 0.020). However, no significant difference was seen in SOD1 activity between male placebo and male DML groups (P = 0.203). In this study, MDA level, a product known for lipid peroxidation, was measured in humans. MDA levels were reduced in the DM group compared to the placebo group, consistent with previous studies. DM group shows significant increase in SOD levels in the cancer treatment group than female placebo group. This demonstrates that DM extract treatment increases the antioxidant capacity of blood. In conclusion, the DM administration has a positive effect on Cd and Hg excretions in the serum and increases the antioxidant capacity by decreasing the MDA level and increasing the SOD activity in the serum (Table 1).

There are two study in the similar in vivo experiments. First, this study is the antioxidant effect of mouse hippocampus exposed to mercury on the extracts of DM.[13] A total of 21 rats were divided into control, DML (100 mg/kg), MeHg (5 ug/kg) and DML-MeHg for a total of 4 weeks. To

Table 2. In vivo study lists

References	Active part of DM	Cell name	Outcome measure	Result
Hyun et al.[7]	Branches, debarked stems, bark, and two different stages of leaves, methanolic extract	Colon adenocarcinoma cells (COLO-205), clonal human osteosarcoma cells (HOS), biliary tract cells (SNU-245 and SNU-308), and hepatocellular carcinoma cells (Huh-BAT and Huh-7)	DPPH radical-scavenging activity, ferric-reducing ability power assay, cytotoxic activities, total phenol and flavonoid contents, reducing power activity, cell viability assay, cell morphology, Huh-7 cell migration, apoptosis and senescence detection, immunoblotting	DbSE displayed a stronger ability to decrease DPPH radicals (RC_{50} = 16.7 lg/mL) than other organ extracts. DbSE, yellow leaves extract (YLE, RC_{50} = 31.6 lg/mL) and green leaves extract (GLE, RC_{50} = 37.8 lg/mL) showed higher radical scavenging activity than BHT (RC_{50} = 40.1 lg/mL). The reducing power of each extract and BHT on Fe^{3+} was concentration-dependent. The methanolic extracts from the bark (bark extracts) ($P < 0.001$) and branches (debarked stem extracts) ($P < 0.001$) revealed the lowest anti-oxidant activity, whereas DbSE had a relatively higher reducing power than the other samples.
Chung et al.[10]	The DM yielded 0.72% (v/w), essential oil with a foul odor.	-	Serum TC, TG, HDL-C levels	DMEO dose-dependently reduced the serum TC (control 80.1 ± 2.3 vs. DMEO 77.2 ± 1.9), LDL-C (control 22.2 ± 2.0 vs. DMEO 15.8 ± 3.7), and TG (control 77.2 ± 5.3 vs. DMEO 70.2 ± 3.8) levels.
Kim et al.[12]	DML, 94% (v/v) ethanol solvent	Oral microbes C. albicans, *Streptococcus mutans*, normal human oral keratinocyte obtained from Science Cell Research Laboratories	Antiproliferative activity of solvent fractions (paper disc method), antioxidant capacity using DPPH radical scavenging assay	DM extracts showed antibiotic effects against *Streptococcus mutans* and *Candida albicans* at 40, 80, 100 μg/mL (a diameter of 2.0-3.5 mm). The n-hexane fraction showed a much higher antibiotic activity compared to other fractions; the antibiotic activity against *Streptococcus mutans* from extract concentrations of 20, 40, 80, and 100 μg/mL resulted in clear zone diameters of 1-1.5, 1.5-2.3, 2-2.5, and 2.3-3 mm. The antibiotic activity against *Candida albicans* from extract concentrations of 20, 40, 80, and 100 μg/mL resulted in clear zone diameters of 0.5, 1.0, 1.0-1.5, and 1.5 mm wider, respectively. Antioxidant capacities of the DML extracts (82.92 ± 0.49%) at the same concentration of 500 μg/mL. DML extracts retained a high cell viability (60-100%); the effective concentration ranges without affecting the survival rate was 2.5-10 μg/mL, then that of the control group. The remaining concentration groups (25-40 μg/mL) displayed a survival rate of approximately 70%.
Akram et al.[16]	methanolic extract	RAW 264.7	MTT assay, nitrite, PGE2, and cytokine production, Western blot, PCR, acetic acid-induced writhing response test	Methanolic extract of DML significantly and dose-dependently reduced the production of NO and PGE2 in LPS-induced RAW 264.7 macrophages.
Yu et al.[17]	-	RAW 264.7 murine macrophage cells	MTT assay, NO, PGE2, RNA, DNA, NF-κB reporter, immunofluorescence analysis	NO and PGE2 production was markedly induced in LPS-stimulated RAW 264.7 macrophages when compared to unstimulated negative controls, while pretreatment with oleifolioside. A significantly prevented this increase, in a dose-dependent manner.

Table 2. Continued

References	Active part of DM	Cell name	Outcome measure	Result
Jin et al.[21]	-	A 549 human lung carcinoma cells	Oleifolioside B, apoptotic cell (flowcytometric analysis), DNA fragmentation assay, caspase activity, MDC staining, immunocytochemistry	Treatment with OB significantly reduced cell viability in a concentration- and time-dependent manner (cell viability: 25, 30, 35, 40 Um, time 12, 18, 24 hours) ($P < 0.05$). Treatment with OB time-dependently induced DNA fragmentation, a hallmark of apoptosis, in a time-dependent manner. Exposure to OB led to a significant reduction in the anti-apoptotic protein cIAP-2, survivin and c-FLIP in a time-dependent fashion. OB treatment resulted in a time-dependent increase in the level of the pro-apoptotic FasL proteins and caused time-dependent downregulation of the whole form of the Bid proteins, which reflects Bid cleavage and activation. The active forms of caspase-3 and -8 increased and the expression of procaspase-9 decreased in a time-dependent manner following OB treatment. Treatment with OB resulted in a time-dependent increase in caspase activity (-3, -8, and -9) compared with the control cells, which was associated with the progressive proteolytic cleavage products of PARP, an activated caspase-3 substrate protein (12 hours, -3, -8; $P < 0.05$/ 18 hours, -3, -8; $P < 0.05$/ 24 hours, -3, -8; $P < 0.05$). Flow cytometric analysis also revealed that treatment with OB increased the accumulation of cells at the apoptotic sub-G1 phase in a time-dependent manner (12, 18, and 24 hours; $P < 0.05$). A 549 cells were pretreated with z-VAD-fmk, a broad-spectrum caspase inhibitor, for 1 hour, followed by treatment with 30 μM OB for 24 hours.

DM: *Dendropanax morbifera*, DML: *Dendropanax morbifera Léveille*, DPPH: 1-diphenyl-2-picryl-hydrazyl, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, MTT: tetrazolium-based colorimetric, PGE2: prostaglandin E2, PCR: polymerase chain reaction, NO: nitric oxide, RNA: ribonucleic acid, DNA: deoxyribonucleic acid, NF-κB: nuclear factor-κB, MDC: monodansylcadaverine, DbSE: debarked stem extracts, BHT: butylated hydroxytoluene, DMEO: *Dendropanax morbifera* essential oil, LDL-C: low-density lipoprotein cholesterol, LPS: lipopolysaccharide, OB: obestatin, cIAP-2: cellular inhibitor of apoptosis 2, c-FLIP: cellular FLICE-inhibitory protein, FasL: Fas ligand, PARP: poly (ADP-ribose) polymerase 1

confirm antioxidant activity, MDA levels, reactive oxygen species (ROS) and SOD1 were measured. As a result, Hg concentration was significantly decreased to 75.4% in the MeHg group ($P < 0.05$). The intensity of dichlorofluorescein fluorescence and MDA levels were significantly decreased ($P < 0.05$) in the DML-MeHg group. There were significant increase in SOD1 and glutathione peroxidase (GPx) activities with 94.9% and 93.8%, respectively ($P < 0.05$). These results show that the leaf extract of DML has a strong antioxidant effect in the hippocampus of mice exposed to mercury. The following article also suggests that when the extract of DM is administered, the oxidative damage of the hippocampus is prevented by increasing the antioxidant levels in Cd exposed rats.[14] Control groups, DM stem extract (DMS), Cd-, and Cd-DMS treated rats (n = 7 in each group) were divided into groups for Cd concentration measurements in blood, brain, and kidney tissue. Similarly, several antioxidant markers were measured in this study. The MDA concentration in the Cd-DMS group was significantly reduced (74.4%) in the Cd-treated group ($P < 0.05$). Compared to Cd-treated group, the MDA level of the Cd-DMS group was significantly lower (39.1 nmol/mg protein) ($P < 0.05$). Compared to Cd treated group ($P < 0.05$), the protein carbonyl level was significant decreased to 57.4% in Cd-DMS group. GPx activities were significantly higher in the Cd-DMS-group than the Cd-treated group, and the greatest increase was seen in GPx activity ($P < 0.05$). There were significant increases in the thyroid stimulating hormone level and glutathione reductase activity to 172.9% and 174.7%, respectively. Activity of glutathione S-transferase (GST) was significantly decreased in the Cd-DMS-treated group ($P < 0.05$). In this paper, it was confirmed that DMS administration promotes the excretion of Cd in the kidney and alleviates ROS, lipid peroxidation, and Cd-induced increase, which are altered by oxidative stress. DMS also reduced Cd-induced oxidative stress in hippocampus (Table 1).

In other in vitro experiment, antioxidant activity of methanol extracts of DM were investigated.[7] It was revealed that the methanol extract of DM leaves and stem was the source of antioxidant compounds and showed possibility to be developed as a botanical drug in the future. According to Chien et al.,[15] (9Z,16S)-16-Hydroxy-9,17-octadecadiene-12,14-diynoic acid (HODA) enhanced nuclear factor (NF) E2-related factor 2 (Nrf-2) activation and its downstream antioxidant gene heme oxygenase-1 (HO-1), we could confirm that HODA has significant antioxidant activity.

Anti-inflammatory Activity

Menopause is also associated with inflammation, along with oxidative stress. The risks of inflammations are increased in accordance with the loss of estrogen during postmenopausal period. DM helps to strengthen immune cell growth and early immune system and defense system against causes causing various diseases. One of the known efficacies DM extract is anti-inflammatory activity. Inflammation is a defensive period that prevents damage to the human body caused by infection. It is accompanied by symptoms such as development, fever and pain.

There is an in vitro experimental study confirming anti-inflammatory activity when the DM extract was administered. DM extract showed the strongest inhibitory effect on inflammatory mediators and cytokines in macrophages. This effect is due to inhibition of NF-κB nuclear translocation and phosphorylation of c-Jun N terminal kinase 1/2 and Nrf-2/HO-1 activation. According to these experimental results, it can be understood that the extract of DM has anti-inflammatory and analgesic effects.[16] Also, in Yu et al.,[17] a new triterpenoid compound, isolated from DM, strongly inhibits the production of lipopolysaccharide (LPS)-stimulated nitric oxide (NO) and prostaglandin E2 in RAW 264.7 cells. Consistent with these results, oligopoly side A dose-dependently inhibited the expression of LPS-stimulated inducible NO synthase (iNOS) and cyclooxygenase-2 at both protein and mRNA levels NF-κB DNA binding activity and transcriptional activity. These results indicate that olefolioside A can be developed as an anti-inflammatory agent that can target both NF-κB and mitogen-activated protein kinase signaling pathways (Table 2).

A similar case report was published using DM extract. According to the case reports,[18,19] in this paper, it was confirmed that the extract of DM showed anti-inflammatory activity that can effectively inhibit NO production in LPS-induced macrophage inflammation analysis. HODA in the leaves of DM significantly inhibited the production of NO in

RAW 264.7 cells. Also, mRNA and protein expression levels of iNOS were also dose-dependently inhibited by HODA. HODA also reduced the transfer of NF-κB to the nuclear fraction. On the other hand, HODA enhanced Nrf-2 activation and its downstream antioxidant gene HO-1. We conclude that HODA has significant anti-inflammatory and antioxidant properties. Such DM compounds are potentially developable as chemical prophylactic agents. According to another study,[15] HODA isolated from the leaves of DM inhibited NO production in LPS-induced RAW 264.7 rat macrophages (IC50 = 4.28 μM). There is a study showing that production significantly inhibited (Table 1).

Anti-thrombotic

It is likely that coagulation factors are changed and the peripheral blood flow decreases as the body ages. One study examined the antithrombotic effect of rutin on fibrin and blood coagulation, coagulation and platelet activation in DM and examined the antithrombotic effect on the thromboembolism mouse model (Table 1).[20] Experimental results show that the rutin inhibits blood clot formation. Urokinase plasminogen activator inhibited 85% of blood clotting at 50 IU and Rutin inhibited 60% of blood clotting at 50 mg (0.27 mM). Other studies have shown that both renal tubular in vitro and mouse models significantly restored acute renal failure by cisplatin.[11] The activity against rutin in the DM compound was confirmed. As a result of the experiment, the inhibition of fibrin clot formation was measured by the weight of the remaining fibrin clot. The inhibition of fibrin clotting was significantly inhibited at routines 5, 10, 20, and 50 mg compared to the untreated control. Thromboembolism model of thrombin induced rat. In addition, 20 mg/kg of aspirin showed a protective effect of 50% to 60%. The mechanism of the kidney protection effect of DM extracts was antioxidant, mitochondrial preservation and anti-apoptotic activity. Also, it is shown that rutin, one of the compounds of the DM, can act as an antithrombotic agent for cardiovascular diseases.

Anti-cancer Activity

The risks of ovarian cancer, uterine cancer, etc. increases once women reaching menopause. According to the results of previous studies, yellowtail components exhibit various pharmacological activities such as anti-complement, anti-diabetic and anticancer effects. Recently, oleifolioside B, a component of DM, in A549 non-small cell lung cancer cells was first studied for the anticancer mechanism leading to apoptosis and autophagy.[21] In this paper, exposure to oleifolioside B led to typical features of caspase activation and apoptosis, and the pan-caspase inhibitor carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone (Z-VAD-FMK) not prevent apoptotic cell death. This suggests that oleifolioside B induced apoptosis is irrelevant to caspase activation. However, pretreatment of the autophagy inhibitor bafilomycin A1 attenuated OB-induced apoptosis and dephosphorylation of Nrf-2. These results suggest that the function of oleifolioside B-induced autophagy as a death mechanism in A549 cells and oleifolioside B is likely to be an anticancer agent targeting apoptosis and autologous cell apoptosis and the Nrf-2 signaling pathway. According to another article,[7] there is a paper analyzing the antioxidant activity and anticancer potential of various tumor cell lines including colon adenocarcinoma cell (COLO-1). Clone human osteosarcoma cell HU, biliary tract cells (designated SNU-245 and SNU-308), and hepatocellular carcinoma cells (Huh-BAT and Huh-7). In particular, it was confirmed that apoptosis and aging cells were increased in Huh-7 cells. Treatment with a peeled stem extract for 24 hours strongly induces p53 and p16, while both leaf extracts inhibited extracellular signal-regulated kinase (ERK) activation. Peeled stem and green leaf extract also reduced Akt levels in Huh-7 cells and activated the p16 and p53 pathways. Confirming that it suppresses Huh-7 cell proliferation with inhibition of Akt or ERK signaling. To develop DM extract, a wide range of pharmacological and clinical investigations should be the main focus. It is suggested that methanol extracts from leaves and peeled stem are the source of anticancer compounds and can be developed as botanical drugs. Also, there are various studies on apoptosis related to DM extract.[22~25] The above papers are a thesis that the extract of DM is related to apoptosis in various cell lines (Table 2).

Conclusion

Aging-associated symptoms such as decline in antioxidant levels, inflammations are generally seen in postmenopausal women. Postmenopausal women are vulnerable to various diseases and cancers including osteoporosis, diabetes, ovarian/uterine cancers, etc. due to loss of estrogen level as the body ages. This review article suggests that DM extracts has medicinal effects on postmenopausal and aging related symptoms contributed by their antioxidant, anti-inflammatory, anticoagulant, and anti-cancer activity. DM extracts, one of health functional foods from natural materials, have a variety of potential therapeutic effects in many diseases associated with aging and hormonal changes after menopause. In particular, DM has a lot of routines. Routine is a type of flavonoid-based flavonoid glycoside that is known to play an important role as much as vitamin C. Routine is a substance similar to quercetin and has anticancer, anti-inflammatory, anti-allergic and anti-virus effects. The needs for health functional foods are increasing in aging society that elderly women aged ≥65 years account for over 20% of the Korean population. Further researches and development of DM extracts are required for the prevention and treatment of aging and postmenopausal symptoms.

Acknowledgement

This research was supported by High Value-added Food Technology development program, Ministry of agriculture, Food and Rural Affairs, Republic of Korea (116029-03-2-HD040).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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