

Effect of Some Medicinal Plants Extract on Monosodium Glutamate induced Uterine Fibroid: A Review

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Abstract: Uterine fibroid is a non-malignant tumour that are most commonly presented in women of reproductive growth age. Clinical symptoms that frequently manifested are heavy menstrual bleeding, recurrent pregnancy loss and subfertility. The causes of development of fibroid is not well understood but strong evidence supported that one of the causes is the combination of action of progesterone and estrogen. Administration of Monosodium glutamate (MSG) for long period of times has reported to induced uterine fibroid in female Wistar rats. Research reviewed includes clinical manifestation, statistics and treatment with types of substance abuse and meeting future challenges in Malaysia. Therefore, medicinal plants extract has been used as an alternative approached to treat uterine fibroid compare to surgical procedures. This review is an effort to update the medicinal plants extract used worldwide to treat uterine fibroid.

Keywords: Monosodium glutamate, traditional plant, uterine fibroid

1. INTRODUCTION:

Uterine fibroid or leiomyomas is one of the most common benign tumour of uterine smooth muscle in women¹. Uterine fibroid can be classified according to their location; submucous, intramural, subserosal and pedunculated fibroid and the symptoms varies according to the size and location of the fibroids². Most of women do not have distinct symptoms but they can be associated with following symptoms such as abnormal uterine bleeding, anemia, pain area of pelvic, bladder impairment, bulk effects on adjacent structure in pelvis, recurrent pregnancy loss, and subfertility³.

In United States the prevalence of fibroid cases identified by diagnostic methodology ranges between 4.5% to 68.6% depending on the study population. The estimated cumulative incidences of fibroid cases from ultrasonography findings showed, women age less than 50 years is significantly higher for black women (>80) compare to white women (~70)⁵. In Malaysia, the number and discharge rate in Ministry of Health Hospital due to leiomyoma of uterus are increasing from year 2017 – 2018 with 8.23 discharge rate (per 100 000 population) in 2017 and followed by 2018 with 9.61⁵. In addition, the number of death and mortality rate due to leiomyoma also increase from 0 cases in 2017 to 4 death cases in 2018 in Ministry of Health Hospital⁵.

Although, the number of discharge and rate because leiomyoma of uterus decreases in year 2016 and 2017 from 9.05 to 8.23 of discharge rate but diseases due to neoplasms still holds top 4 principal causes of death in Ministry of Health Hospital with 11.99% and number one

principal causes of death in Private Hospital with 29.66% in year 2017⁶. Besides, limited data related to prevalence and incidence of uterine fibroid in Malaysia is suggested by insufficient public awareness of fibroid and the future health results among women⁷⁻⁹.

It is recommended for future studies to use medicinal plants as a treatment of uterine fibroid since the current medicinal treatments such as hormone replacement therapy is only effective for 6-12 months. This is because of the significant side effects develop from long term usage¹⁰. Although, surgical methods such as uterine artery embolization and high intensity focused ultrasound ablation can be used¹¹. However, both the addition cost and adverse effects occur still suggests orthodox drugs for a better treatment option. A study also showed non-surgical treatment is preferable compare to surgical methods since only women with poor quality of life seeks for hysterectomy as a permanent treatment¹².

2. EFFECT OF MONOSODIUM GLUTAMATE ON UTERINE FIBROID

Monosodium Glutamate (MSG) is one of the most common used food additives which help to build up taste and act as preservations¹³. In Japanese locality, the taste is described as umami which defined as 'savory'¹⁴. They are reports indicate that MSG may cause pathological effects on different systems in humans such as central nervous system, cardiovascular system, obesity and metabolic disturbances, reproductive system and other effects to human system¹⁴. For instance, previous study reported MSG has toxic effect on the testis by causing significant oligozoospermia and increase abnormal sperm morphology in a dose-dependent fashion in male Wistar rats¹⁵. MSG also shown to influence levels of total protein, cholesterol and estradiol in MSG induced uterine fibroid in rats¹⁶. Studies have also shown that MSG induces uterine fibroid in rats by increasing the levels of total protein, cholesterol and estradiol¹⁶. Hence,

this review is an effort to update the medicinal plants extracts used as an alternative to treat MSG induced uterine fibroid.

Monosodium glutamate (MSG) is a sodium salt occurring L-form of glutamic acid. The average individual intake of MSG in United Kingdom general population in 1991 was 580mg/day and 4.68g/day for extreme users¹⁷. Although the amount of MSG in foods defers according to individual's taste preference but the estimated average daily intake of MSG per person in industrialized countries is 0.3-1.0g¹⁸. The oral dose that is lethal to 50% of subjects (LD50) in rats and mice is 15.000-18.000 mg/kg body weight¹⁹.

The study done by Kuffuor et al. (2013) showed the administration of MSG via oral gavage for 30 days in adult female Wistar Rats has caused formation of uterine fibroid. The level of total cholesterol, total protein, progesterone, estradiol (estrogen), uterus weight and size showed an increased which indicates induced fibroid in rats²⁰⁻²³.

The administration of MSG with different dosage 200 mg/kg and 900 mg/kg body weight shown to have adverse effect towards the histology of pituitary gland and changes in follicular and luteinizing hormone levels after given MSG daily for 50 days²². In addition, they are also abnormal changes in the uterus gross morphology, histology and the levels of MMP2²³.

Administration of MSG for long period of time also result in abnormal changes in histological structure of uterus such as disorganized extracellular matrix which mainly consists of varies subtypes of collagen, fibronectin, proteoglycans, hyperplasia due to cellular proliferation of inflammatory cells around oocytes and zonal granulosa layer^{22;24;25}. Some cellular hypertrophy of columnar epithelium, distortion of basement separating the endosalpinx and myosalpinx. They were also marked vacuolations and lysed red blood cell appearing in the stroma cells²⁶.

The mechanism of dose dependent hyperplasia effect suggested uterine proliferation has been linked to periods of estrogen secretion because of their increase response to estradiol²³.

Estradiol is specific in uterine cell proliferation which binds to ER α receptors that abundantly presence in the uterus. The interaction between the complex form between the binding of estrogen and ER α receptors and DNA of the nucleus result in activation of enhancer elements in charge of gene expression and transcriptional promoter²⁰. The increased level of estrogen may also be influenced by the activation of enzyme aromatase which acts as a catalyzed between the conversion of testosterone to β -estradiol. This will further result in increased of estradiol synthesis activity²².

3. EFFECTS OF MEDICINAL PLANT ON UTERINE FIBROID

Medicinal plants play a vital role as a valuable source in the search for suitable active compounds and their pharmacological properties²⁷. According to Burkill, (1935) more than 1300 medicinal plant species have been recorded in Peninsular Malaysia alone. However, very few studies of medicinal plants can be found related to the pharmacological activities on uterine fibroid especially Malaysian medicinal plants. Thus, this study was carried out to evaluate and compare the effects of medicinal plants that possesses anti-fibroid activity on uterine fibroid.

i. *Drymaria cordata*

Drymaria cordata (Linn.) Willd (Caryophyllaceae) are commonly found scattered in damp places all over the tropics of Asia, Africa and America²⁸. The plant has tendency to grow in dense patches in humid and shady places and also in dry areas with exposure to sunlight. The flowers are green and small in size with slender stems, cordate leaves with short petiole. Based from observations, the plant size and leaf varies in different places. In humid and shady areas, the leaves of the plants may grow up to 2cm large and the succulent. Meanwhile, plants that grow in exposed rocks and sunny areas may have thin and smaller leaves around to 5-7 mm²⁹. They are various pharmacological benefits in the preparation of *Drymaria cordata* such as headache, cold, tumors as fumigant for eye troubles, cerebral stimulant and antifebrile agent²⁸. *Drymaria cordata* extracts also previously has been reported to possesses anti-inflammatory³⁰⁻³², antitussive³³, antibacterial³⁴, cytotoxic³⁵, anxiolytic³⁶, analgesic, anti-nociceptive and antipyretic properties³⁷⁻³⁹.

In a study by Olowofolohan et al using *Drymaria cordata*, co-administration of methanol and chloroform extract at doses 200 and 100 mg/kg body weight respectively for twenty eight days, single dose daily improves the effects of the female virgin rates when administered with Monosodium glutamate (MSG)-induced uterine fibroid days using oral gavage. The methanol and chloroform extract significantly reduced the serum level estrogen, progesterone and total cholesterol when compared with MSG-treated group with chloroform extract have higher effect²². Besides that, the methanol and chloroform extract reduced the cell counts density by 39% and 56% respectively compared to the MSG-treated group²².

ii. *Ginger rhizomes*

Zingiber officinale roscoe is the common name of ginger and most frequent used spices in the world³⁹. It was used as a traditional herbal medicine for the treatment of inflammatory diseases and pain⁴⁰. The rhizome of the ginger which located at the vertical portion of the root is the most commonly used part and studies have shown that ginger extracts possessed different pharmacological effects such such anti-inflammatory⁴¹, anti-oxidant⁴², and anti tumor effects⁴³.

One of the most significant active compounds are gingerols found in fresh ginger and slightly presence in dry ginger. Gingerols are reported to possesses various pharmacological activities such as anti-oxidant⁴⁴, antitumor⁴⁵⁻⁴⁶ and anti-inflammatory activities. Another active compound is paradol which act as anti-oxidant and anti-cancerous properties⁷⁻⁴⁸. Shogaol also has anti-inflammatory activities and anti-oxidant effects⁴⁹⁻⁵⁰. Followed by 6-shogaol that

possesses anti-proliferation activity, anti-invasion and anticancer activities by reducing the expression of matrix metalloproteinase-9 as a result inhibits cell invasion⁵¹⁻⁵².

In a study conducted by Olanrewaju et al., (2017) showed a reverse effect of MSG-induced fibroids towards the histology of pituitary gland and the levels of hormones for both follicular stimulating hormones and luteinizing hormones after the administration of aqueous extract of ginger at different dosage 500 mg/kg, 900 mg/kg and 1700 mg/kg for 50 days²⁴. Meanwhile, a surge in the level of estradiol (estrogen) and progesterone can be observed in only MSG-induced fibroid group⁵³.

Based from the findings of previous study showed group treated with MSG only and low dose ginger extract (500mg/kg) exhibit degenerative alteration with presence of inflammatory and red blood cells^{24;26}. In addition, the increase in weight of the uterus and total body weight in induced rats has result in multiplication of extracellular matrix, deposition of collagen, amyloid and surge level of Matrix Metalloproteinase-2 (MMP-2). The ability of the aqueous extract of ginger rhizomes at high dose nearly diminish the effects of uterine fibroid has proposed another further study between the relationship of uterine fibroid and the pituitary gland due to medicinal plants ability in preventing and protecting the prophylactic effects²⁴.

iii. *Allium sativum*

Garlic (*Allium sativum L*) is a common used spice in foods and possesses pharmacological effects such as antibiotic and antifungal activities⁵⁴⁻⁵⁵. Garlic shown to have widely antibiotic spectrum against both gram negative and gram-positive bacteria, reduce level of cholesterol and blood pressure, helps in preventing cancer, and boost immune system together with anti-oxidant effects⁵⁶. Another pharmacological property of garlic includes inhibition of cell growth of tumour and prevention of chemo effects⁵⁷. The garlic and their constituents shown to help in inhibiting the growth of chemical induced tumor in liver⁵⁸, colon⁵⁹, prostate⁶⁰, bladder⁶¹, mammary gland⁶², esophagus⁶³ in both rodent and human studies. For instance, sulphur that contains alicing, diallyl disulphide (DADS) and diallyl trisulphide (DATS) are another constituents found in garlic that is vital in garlic's pharmacological activities⁵⁵⁻⁵⁶.

The study conducted by Obochi et al. (2009) showed administration of aqueous garlic extracts with dose of 100 mg/kg administered via gastric intubation for 60 days has reduce the effects by MSG almost completely. The level of estrogen (estradiol), serum total protein and cholesterol was significantly lower when compared to MSG only animals group by 54%¹⁶.

Furthermore, the findings of another study also corresponds by which there is a reduction of total cholesterol, total protein and the level of estradiol (estrogen) in treatment group rats with 100mg garlic extract per kg body weight after the administration of MSG to induced uterine fibroid in Wistar rats¹⁶.

iv. *Blighia unijugata (Sapindaceae)*

Blighia unijugata (Sapindaceae) is a widespread in tropical Africa, extending from Guinea Bissau eastwards to Ethiopia and South Africa⁶⁵. It is recognized for its sedative and analgesic properties in the treatment of rheumatism⁶⁶. The roots are used to treat post-partum bleeding (haemorrhage) and boils, meanwhile the seeds are used to treat vomiting⁶⁷.

Study done by Koffuor et al. (2013) showed the administration of ethanolic stem bark of *Blighia unijugata (Sapindaceae)* extract at different dosage 50 and 100 mg kg⁻¹ for 30 days significantly decreases the elevated levels of plasma cholesterol, estradiol as well as uterus size and weight suggesting the efficacy as anti-fibroid agent²⁰. The lethal dose was less than 1000 mg kg⁻¹ per os. It was reported ethanolic stem barks of *Blighia unijugata* had more phytochemicals presences compared to aqueous and petroleum stem bark *Blighia unijugata* extract. Secondary metabolites found were triterpenoids, glycosides, saponins and

phytosterols. They suggested ethanolic stem bark of *Blighia unijugata* (*Sapindaceae*) extract had better therapeutic value than aqueous stem bark of *Blighia unijugata* extract and petroleum stem bark *Blighia unijugata* extract.

v. *Cyperus rotundus L*

Cyperus rotundus L. is dried rhizome group in the genus family of Cyperaceae and shown to have strong with slight bitter sweet and bland taste⁶⁸. The common usage of this plant is to treat hernia pain, spleen, stomach and irregular menstruations⁶⁹. *Cyperus rotundus L.* are composed of four bioflavone constituents; amentoflavone, ginkgetin, isoginkgetin and sciadopitysin⁷⁰. Bioflavone constituents possesses anti-inflammatory, anti-viral and anti-tumor properties⁷¹.

In a study by Ju and Xiao (2016) showed the high-dose amentoflavone when administered intragastrically for 42 days once daily showed inhibitory effect on uterine hyperplasia in rats when using different dosage: 15 g/kg, 10 g/kg and 5 g/kg respectively. The high dose amentoflavone decreased the uterine coefficient, serum estradiol, serum progesterone concentration, uterine homogenate nitric oxide synthase (NOS) and pathomorphological changes such as uterine smooth muscle hyperplasia was improved. Besides that, the result of Bcl-2 expression was significantly decreased⁶⁸.

4. MECHANISM OF MEDICINAL PLANT ON UTERINE FIBROID

i. *Drymaria cordata*

A study by Olowofolahan et al., in 2017, suggest bioactive agents found both in MEDC and CFDC able to ameliorate hyperplasia or tumor result from MSG-induced uterine and the suggested mechanism is via inhibition of aromatase enzyme²². It was reported that, the chloroform fraction of methanol extract of *Drymaria cordata* (CFDC) is a potent inducer of mitochondrial-mediated apoptosis and this could be relevant in management and treatment of diseases in which upregulation of apoptosis is needed²⁴.

Papers on the mechanism of *Drymaria cordata* as anti-fibrotic activity against uterine fibroid are scanty. Therefore, further studies to determine the exact mechanism of medicinal plant as anti-fibrotic activity against uterine fibroid need to be concluded.

ii. *Ginger rhizomes*

Study done by Olenrewaju et al. (2017) suggested the aqueous extract of ginger prevented and reversed MSG-induced formation by affecting the hormone estrogen, progesterone, hormone receptors and the circulating enzymes. It promotes fibroid formation by aberrant expressed aromatase and 17-beta-hydroxysteroid dehydrogenase, which convert circulating androstenedione into estradiol⁷². Estradiol action is control by their nuclear receptors ER α and ER β and this will leads to an increase in synthesis of progesterone receptor (PR). As a result caused an increased in secretion of progesterone hormone by the ovaries. Estrogen also modulates the growth of fibroid by altering few growth factors such as; up-regulation of Transforming Growth Factor-b3, Insulin Growth Factor-1, Epidermal Growth Factor Receptor and this as result caused disturbing apoptosis of cell and changing the survival of leiomyoma cells⁷³. Through up-regulation EGF, TGF-beta1 and TGF beta 3 by progesterone promotes growth of leiomyoma. Meanwhile, through up-regulating Bcl-2 expression and down-regulating TNF-alpha by progesterone caused survival of leiomyoma⁷⁴⁻⁷⁵. Both estrogen and progesterone together promotes cell proliferation, prolonged survival of leiomyoma cells and enhances extracellular matrix formation by up-regulation of TGF-B3 and down regulation of p53⁷⁶. However, the exact mechanism to cause fibroid is still not clear but it was reported both estrogen and progesterone has a vital role in the fibroid growth.

iii. *Alium sativum*

Study done by Obochi et al. (2009) showed garlic able to improve the imbalances of estrogen metabolism that is linked with abundance of catechol estrogen and surge of inflammatory prostaglandin. This is suggested, if estradiol (estrogen) and estrone are not properly eliminated, it could damage some tissues that may eventually be expressed as cancer⁶⁴. The garlic extract also promotes the synthesis of gonadotrophins and ovarian hormones and inhibits the proliferation of cancer cells¹⁶.

iv. *Blighia unijugata* (Sapindaceae)

Koffuor et al. (2013) suggested the ethanolic stem bark of *Blighia unijugata* extract reversed the MSG-induced hyperplasia in animals by reducing cholesterol and biochemical markers of protein synthesis. It was reported that the uterine proliferation has also been linked to periods of estrogen secretion because of their increased response to estradiol⁷⁶. They concluded the decreased level of estradiol by effect of EBU would decrease uterine proliferation²⁰.

Papers on the mechanism of ethanolic stem bark of *Blighia unijugata* extract as anti-fibrotic agent against uterine fibroid are scanty. Therefore, further studies to determine the exact mechanism of medicinal plant as anti-fibrotic agent against uterine fibroid need to be concluded.

5. CYPERUS ROTUNDUS L

Xiao and Jun. (2016) reported amentoflavone able to inhibit the incidence of uterine fibroids by up-regulating Bax expression and down-regulating Bcl-2 expression. The study revealed, Bcl-2 expression in uterine leiomyoma tissue was significantly high in uterine muscle tissue of blank group and this result of the up-regulation expression of Bcl-2. The apoptosis mechanism was prevented due to down-regulated expression of Bax and high expression of Bcl-2 and leads to the inhibition of apoptosis⁷⁸⁻⁷⁹ and apoptotic disorders of muscle cells. However, the study suggested other mechanism of action to cause fibroid need further research.

6. CONCLUSION

The review summarised the monosodium glutamate activity induced uterine fibroid and the effect of medicinal plants to treat MSG-induced uterine fibroid. The rising of cases of uterine fibroid should be dealt with in order to improve women health condition and social development. Further research need to be carried out explore the vast possibilities and anticipate the positive outcome using medicinal plants to curb this phenomenon.

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