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# The effects of *Myristica fragrans* on fertility

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requirement**

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بسم الله الرحمن الرحيم  
و إذا مرضت فهو يشفين  
صدق الله العظيم

سورة الشعراء  
الايه 80

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# **Dedicated**

**To my family  
for their endless love support and encouragement  
To my source of confidence and power  
my real one friend and soul mate ..**

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## List of abbreviations :

FSH ..... Follicle-stimulating hormone  
LH .....Luteinizing hormone  
SFA..... Seminal fluid analysis  
MF..... Myristica Fragrans

## Abstract

- **Background :** Infertility is “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.”... (WHO-ICMART glossary<sup>1</sup>).
- “Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. The male partner can be evaluated for infertility or subfertility using a variety of clinical interventions, and also from a laboratory evaluation of semen

**Aim of study :** the effect of Myristica Fragan on fertility in males

Patients and methods: a prospective study involved taking data from 20 male patients in Al-Kadhimya Teaching hospital during the interval (November 2018 – march 2019) , the data included the age, medical conditions , and seminalfluid analysis before and after treatment .

**Results:** the SFA of the patients regarding ( conc. , Motility , and morphology ) was improved after treatment especially the concentration. and level of FSH in 1.7-6.85 miu/ml improved more , the level of LH in 1.1-4 miu/ml improved more , testosterone in 2.27-6.29 ng/ml improved more

**Conclusion :** Most improved age group was (20-30), FSH, LH and testosterone improved , Parameters of SFA ( conc. , Motility , and morphology ) improved

## Chapter one

# Introduction

## Background

Infertility is the failure to conceive (regardless of cause) after 1 year of unprotected intercourse. This condition affects approximately 10-15% of reproductive-aged couples.<sup>(1)</sup>

## Primary vs. secondary infertility

Primary infertility is defined as the absence of a live birth for women who desire a child and have been in a union for at least 12 months, during which they have not used any contraceptives <sup>(2)</sup>

The World Health Organisation also adds that 'women whose pregnancy spontaneously miscarries, or whose pregnancy results in a still born child, without ever having had a live birth would present with primarily infertility <sup>(3)</sup>

Secondary infertility is defined as the absence of a live birth for women who desire a child and have been in a union for at least 12 months since their last live birth, during which they did not use any contraceptives <sup>(4)</sup>

Thus the distinguishing feature is whether or not the couple have ever had a pregnancy which led to a live birth.



There are Female and male factor infertility

Female factors that affect fertility include the following categories: <sup>(5)</sup>

- Cervical: Stenosis or abnormalities of the mucus-sperm interaction
- Uterine: Congenital or acquired defects; may affect endometrium or myometrium; may be associated with primary infertility or with pregnancy wastage and premature delivery
- Ovarian: Alteration in the frequency and duration of the menstrual cycle—Failure to ovulate is the most common infertility problem
- Tubal: Abnormalities or damage to the fallopian tube; may be congenital or acquired
- Peritoneal: Anatomic defects or physiologic dysfunctions (eg, infection, adhesions, adnexal masses)

Male factors that affect fertility include the following categories: <sup>(6)</sup>

- Pretesticular: Congenital or acquired diseases of the hypothalamus, pituitary, or peripheral organs that alter the hypothalamic-pituitary axis
- Testicular: Genetic or nongenetic
- Posttesticular: Congenital or acquired factors that disrupt normal transport of sperm through the ductal system

Factors that affect the fertility of both sexes include the following:

- Environmental/occupational factors
- Toxic effects related to tobacco, marijuana, or other drugs
- Excessive exercise
- Inadequate diet associated with extreme weight loss or gain
- Advanced age

## **Unexplained infertility :**

In the US, up to 20% of infertile couples have unexplained infertility <sup>(7)</sup>  
In these cases abnormalities are likely to be present but not detected by current methods. Possible problems could be that the egg is not released at the optimum time for fertilization, that it may not enter the fallopian tube, sperm may not be able to reach the egg, fertilization may fail to occur, transport of the zygote may be disturbed, or implantation fails. It is increasingly recognized that egg quality is of critical importance and women of advanced maternal age have eggs of reduced capacity for normal and successful fertilization. Also, polymorphisms in folate pathway genes could be one reason for fertility complications in some women with unexplained infertility <sup>(8)</sup> .

## Diagnosis of infertility

### Medical History <sup>(9)</sup>

Initial questions may include:

- A review of past medical history, prior surgeries and medications used
- A discussion of family history of infertility or birth defects
- A careful review of social history and occupational hazards to evaluate potential exposure to hazardous substances that could impact fertility

### Physical Exam

Next, you will receive a thorough physical examination to evaluate the pelvic organs — the penis, testes, prostate and scrotum.

### Laboratory Tests <sup>(10)</sup>

Laboratory tests may include:

- **Urinalysis** — These can indicate the presence of an infection.
- **Semen Evaluation** — The evaluation assesses sperm motility or movement, the shape and maturity of the sperm, the volume of the ejaculate, the actual sperm count and the liquidity of the ejaculate.
- **Hormonal Tests** — Hormonal tests evaluate levels of testosterone and FSH (follicle-stimulating hormone) to determine the overall balance of the hormonal system and specific state of sperm production. Serum LH and prolactin are other hormonal tests that may be done if initial testing indicates the need for them.

If a diagnosis is not obvious after the initial evaluation, further testing may be required. One or more of the following tests may be recommended:

- **Seminal Fructose Test** — To identify if fructose is being added properly to the semen by the seminal vesicles
- **Post-ejaculate Urinalysis** — To determine if obstruction or retrograde ejaculation exists
- **Semen Leukocyte Analysis** — To identify if there are white blood cells in the semen
- **Kruger and World Health Organization (WHO) Morphology** — To examine sperm shape and features more closely
- **Anti-sperm Antibodies Test** — To identify the presence of antibodies that may contribute to infertility

- **Sperm Penetration Assay (SPA)** — To confirm the sperm's ability to fertilize
- **Ultrasound** — To detect varicoceles (varicose veins) or duct obstructions in the prostate, scrotum, seminal vesicles and ejaculatory ducts
- **Testicular Biopsy** — To determine if sperm production is impaired or a blockage exists
- **Vasography** — To check the structure of the duct system and identify any obstructions
- **Genetic Testing** — To rule out underlying mutations in one or more gene regions of the Y chromosome, or to test for cystic fibrosis in men missing the vas deferens

## Management :

**Counselling** Sometimes certain 'lifestyle' factors may be responsible for poor semen quality: for example obesity, alcohol abuse, use of anabolic steroids, extreme sports (marathon training, excessive strength sports), and 708 G.R. Dohle et al. / European Urology 48 (2005) 703–711 increase in scrotal temperature through thermal underwear, sauna or hot tub use or occupational exposure to heat sources. A considerable number of drugs can affect the spermatogenesis. <sup>(11)</sup>

### Medical (hormonal) treatment

There is no evidence that empiric hormonal therapies, such as human menopausal gonadotrophin (HMG)/ human chorionic gonadotrophin (HCG), androgen, antioestrogens (clomiphene and tamoxifen), prolactin inhibitors (bromocriptine) and steroids, improve pregnancy rates in men with idiopathic OAT. However, some primarily endocrinological pathologies can be treated medically <sup>(12)</sup>

Low testosterone - testosterone substitution is indicated; substitution exceeding normal physiological values has a negative effect on the spermatogenesis - Hypogonadotropic hypogonadism - pulsatile GnRH, i.v. or sc; the usual starting dose is 5 mg, increased if necessary to 10–20 mg, every 90 minutes. Alternatively, HCG 1500 IE and HMG 150 IE (FSH) i.m. twice weekly can be applied. - Hyperprolactinaemia - dopamine agonists In patients with sperm auto-antibodies, corticosteroids are not recommended because of serious side effects and unproven lack of efficacy. A wide variety of empiric drug approaches have been performed

The scientific evidence for empirical approaches is low. Criteria for the analysis of all therapeutic trials have been re-evaluated. There is consensus that only randomised-controlled trials, with 'pregnancy' as the outcome parameter, can be accepted for efficacy analysis. Use of recombinant human follicle-stimulating hormone in patients with idiopathic oligozoospermia with normal FSH and inhibin B may be a debatable choice for the future to improve spermatogenesis. Further studies are necessary. Tamoxifen and testosterone undecanoate appear to increase the natural conception rate in a selection of men with idiopathic oligozoospermia <sup>(13)</sup>

## Surgical treatment <sup>(14)</sup>

**Varicocele** A range of surgical and radiological techniques can be used to treat varicocele. Successful treatment will lead to a significant improvement in semen quality in at least 44% of men treated.

**Microsurgery/epididymovasostomy** Only urologists with experience in microsurgery should undertake this procedure <sup>(15)</sup>. Considering its limited effect on pregnancy rates (20–30%), it is advisable to combine epididymovasostomy with microsurgical epididymal sperm aspiration (MESA), and cryopreserve the harvested spermatozoa for ICSI. The indications for epididymovasostomy include congenital and acquired obstructions at the level of the epididymis, in the presence of a normal spermatogenesis (testicular biopsy).

**Vasovasostomy** Vasovasostomy can be performed either macroscopically or microscopically, though the latter is more effective in improving pregnancy rates. The likelihood of initiating pregnancy is inversely proportional to the obstruction interval and becomes less than 50% after 8 years. Important prognostic factors are the development of antisperm antibodies, the quality of the semen and the partner's age. In approximately 20% of men who have undergone a vasovasostomy, sperm quality deteriorates to the level of azoospermia or extreme oligospermia within 1 year. Poor sperm quality and autoantibodies frequently prevent a spontaneous pregnancy and assisted reproduction is indicated <sup>(16)</sup>

**MESA** MESA in combination with ICSI is indicated when reconstruction (vasovasostomy, epididymovasostomy) cannot be performed or is unsuccessful. An alternative would be percutaneous aspiration of sperm from the caput epididymis (PESA). If a MESA or PESA procedure does not produce spermatozoa or very low numbers of motile spermatozoa, a testicular biopsy can be performed with testicular sperm extraction (TESE) to be used for ICSI <sup>(17)</sup>

**Transurethral incision of ejaculatory ducts or midline prostatic cysts.** Distal obstructions of the genital tract are commonly caused by infections of the prostatic urethra and the accessory glands, or by a cyst in the midline of the prostate. Treatment of the obstruction by transurethral incision of the cyst or the ejaculatory ducts may lead to an increase in semen quality and, occasionally, spontaneous pregnancy <sup>(18)</sup>

# *Myristica fragrans*

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## Description

*Myristica fragrans* is an evergreen tree, usually 5–15 m (16–49 ft) tall, but occasionally reaching 20 m (66 ft) or even 30 m (98 ft) on [Tidore](#). The alternately arranged leaves are dark green, 5–15 cm (2.0–5.9 in) long by 2–7 cm (0.8–2.8 in) wide with [petioles](#) about 1 cm (0.4 in) long. The species is [dioecious](#), i.e. "male" or [staminate](#) flowers and "female" or [carpellate](#) flowers are borne on different plants, although occasional individuals produce both kinds of flower. The flowers are bell-shaped, pale yellow and somewhat waxy and fleshy. Staminate flowers are arranged in groups of one to ten, each 5–7 mm (0.2–0.3 in) long; carpellate flowers are in smaller groups, one to three, and somewhat longer, up to 10 mm (0.4 in) long <sup>(19)</sup>

Carpellate trees produce smooth yellow ovoid or pear-shaped fruits, 6–9 cm (2.4–3.5 in) long with a diameter of 3.5–5 cm (1.4–2.0 in). The fruit has a fleshy husk. When ripe the husk splits into two halves along a ridge running the length of the fruit. Inside is a purple-brown shiny seed, 2–3 cm (0.8–1.2 in) long by about 2 cm (0.8 in) across, with a red or crimson covering (an [aril](#)). The seed is the source of [nutmeg](#), the aril the source of [mace](#) <sup>(20)</sup>

## Morphology

*Myristica fragrans* tree have brown-red bark which is soft, smooth and flakes off in thin layers or large plates. The branching pattern is such that horizontal branches radiate in whorls from the trunk. Leaves (5 to 15 cm × 2 to 7 cm) are simple, entire, 2 ranked and alternately arranged on branches. Leaf veins are pinnate and free or anastomosing or brochidodromous. Leaf blades may be densely pubescent or totally glabrous. *Myristica fragrans* plants are usually dioecious, with the exception of a few monoecious. Flowers are unisexual, inconspicuous, small in size (<4 mm), composed of three sepals (rarely 4) that are fused to varying degrees and exude a strong fragrance <sup>(21)</sup>  
<sup>(22)</sup>

## Biological effects :

In India, spices have been traditionally used since ancient times, for the preservation of food products as they have been reported to have antiseptic and disinfectant properties <sup>(23)</sup>

. Nutmeg is stimulant, carminative, astringent and aphrodisiac; it is used in tonics and electuaries and forms a constituent of preparations prescribed for dysentery, stomach ache, flatulence, nausea, vomiting, malaria, rheumatism, sciatica and early stages of leprosy. Excessive doses have a narcotic effect; symptoms of delirium and epileptic convulsions appear after 1-6 hours <sup>(24)</sup>

It is widely believed that myristicin is the major component responsible for intoxications

Myristicin is toxic when ingested in large amounts, and it is liable to cause fatty degeneration of the liver <sup>(25)</sup>

It was reported that myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene), a naturally occurring allylbenzene found in nutmeg induces cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. Trimyristin shows angiogenic activity <sup>(26)</sup>

Trimyristin and myristicin isolated from *M. fragrans* seeds exhibit good antibacterial activity against Gram-positive and Gram-negative bacteria <sup>(27)</sup>

Grover et al. (2002) <sup>(28)</sup> have studied the pharmacological effects of nutmeg and found that the extracts of nutmeg show a good antidiarrhoeal effect, with a significant sedative property. The extracts also possess a weak analgesic effect, with no harmful effects on blood pressure and ECG

Jan et al. (2005) <sup>(29)</sup> have evaluated the effects of extract of *M. fragrans* and verapamil on the volume and acidity of carbachol induced gastric secretion in fasting rabbits. It has been found that the extract from *M. fragrans* which contains documented natural calcium channel blocker reduces the volume, free and total acidity of gastric secretion. Verapamil also has the same effects. Thus, the effect of *M. fragrans* is similar to verapamil and therefore it can be effectively used in the treatment of peptic ulcer and all other conditions that require calcium channel blockers for the treatment of these disorders.

### Antimicrobial activity

*M. fragrans* (nutmeg and mace) is known to exhibit strong antimicrobial activity against animal and plant pathogens, food poisoning and spoilage bacteria including *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, multi-drug resistant *Salmonella typhi* and *Helicobacter pylori*

Alcoholic extracts of nutmeg show anti-bacterial activity against *Micrococcus pyogenes* var. *aureus* <sup>(30)</sup>. Essential oil of nutmeg caused a significant inhibition of growth and survival of *Yersinia enterocolitica* and *Listeria monocytogenes* in broth culture and in Iranian barbecued chicken

Takikawa et al. (2002) <sup>(31)</sup> have reported the antimicrobial activity of nutmeg (seeds of *M. fragrans*) extract against *Escherichia coli* O157. When the *E. coli*



strains are incubated with spice extract at concentrations of 0.01% and 0.1%, a noteworthy difference has been observed between the O157 *E. coli* and non-pathogenic *E. coli* strains to their tolerance to nutmeg. The populations of the non-pathogenic strains can not be reduced, but those of the O157 strains are remarkably reduced. Antibacterial activity of nutmeg extract was also found against the enteropathogenic *E. coli* O111, but not against enterotoxigenic (O6 and O148) and enteroinvasive (O29 and O124) *E. coli*. When they have examined the antibacterial effect of volatile oils of nutmeg on the O157 and non-pathogenic *E. coli* strains, all O157 strains tested were found to be more sensitive to beta-pinene than non-pathogenic *E. coli* strains. Aqueous extract of nutmeg has bactericidal activity against *Helicobacter pylori*

*H. pylori* infections are associated with the development of gastritis, dyspepsia, peptic ulcer disease, gastric carcinoma and primary gastric B-cell lymphoma. Mahady et al. (2005)<sup>(32)</sup> have studied the in vitro susceptibility of 15 *H. pylori* strains to botanical extracts. It has been found that methanol extract of *M. fragrans* (seed), having a MIC of 12.5 µg/ml against *H. pylori* strains, is highly effective in the treatment of gastrointestinal disorders. Rani and Khullar (2004)<sup>(33)</sup> have reported strong antibacterial activity of methanol extract of *M. fragrans* against multi-drug resistant *Salmonella typhi*. Nutmeg has potent antimicrobial activity against *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 10536) and *Saccharomyces cerevisiae* (ATCC 9763)<sup>(34)</sup>. The volatile oils of *M. fragrans* exhibit considerable inhibitory effects against different genera of bacteria including animal and plant pathogens, food poisoning and spoilage bacteria<sup>(35)</sup>. At 35°C, food-borne pathogen, *Listeria monocytogenes* is extremely sensitive to the oil of nutmeg<sup>(36)</sup>. The two antimicrobial resorcinols malabaricone B [1] and malabaricone C [2] isolated from mace have been reported to exhibit strong antifungal and antibacterial activities

Malabaricone C isolated from *M. fragrans* (nutmeg) irreversibly inhibits Arg-gingipain by 50% at a concentration of 0.7 µg/ml and selectively suppressed *Porphyromonas gingivalis* growth

Macelignan isolated from *M. fragrans* is a potent natural anti-biofilm agent against oral primary colonizers *Streptococcus sanguis* and *Actinomyces viscosus*. These colonizers initially attached to the pelliclecoated tooth surface to form a biofilm. Treatment with 10µg/ml of macelignan caused 30% reduction in growth of these colonies within 5 minute

Cho et al. (2007)<sup>(37)</sup> have isolated three lignans erythro-austrobailignan-6, meso-dihydroguaiaretic acid and nectandrin-B from *M. fragrans* seeds. These lignans were effective against *Alternaria alternata*, *Colletotrichum coccodes*, *C. gloeosporioides*, *Magnaporthe grisea*, *Agrobacterium tumefaciens*, *Acidovorax konjaci* and *Burkholderia glumae* in in vivo and in vitro conditions. Rotaviruses

have been recognized as the major agents of diarrhoea in infants and young children in developed as well as developing countries. Goncalves et al. (2005) <sup>(38)</sup> have studied in vitro anti-rotavirus activity of some medicinal plants used in Brazil against diarrhoea. It was found that the extracts from *M. fragrans* seeds inhibited human rotavirus (90% inhibition) at concentration of 160 µg/ml. Thus *M. fragrans* can be useful in the treatment of human diarrhea, if the etiologic agent is a rotavirus

### Hypolipidaemic and hypocholesterolemic effect

The ethanolic extract of *M. fragrans* (nutmeg) shows hypolipidaemic effect on experimentally induced hyperlipidaemia in albino rabbits. Ram et al. (1996) <sup>(39)</sup> have reported that an oral administration of nutmeg extract at the dose of 500 mg/kg body weight to hyperlipidaemic albino rabbits for 60 days significantly reduced the lipoprotein lipids level. Sharma et al. (1995) <sup>(40)</sup> have reported that administration of *M. fragrans* seed extract to hypercholesterolemic rabbits reduced serum cholesterol and LDL cholesterol by 69.1 and 76.3%, respectively and also lowered cholesterol/phospholipid ratio by 31.2% and elevated the decreased HDL-ratio significantly. It is also known to prevent the accumulation of cholesterol, phospholipids and triglycerides in liver, heart and aorta and dissolves atheromatous plaques of aorta by 70.9-76.5%. Removal of cholesterol and phospholipids in fecal matter is significantly increased in rabbits fed with seed extract of *M. fragrans*.

### Antidepressant activity

Dhingra and Sharma (2006) <sup>(41)</sup> determined the antidepressant activity of n-hexane extract of *M. fragrans* seeds in mice using the forced swim test (FST) and the tail suspension test (TST) at three dose level 5, 10, and 20 mg/kg body weight. The 10 mg/kg dose was found to be most potent, as indicated by the highest decrease in the immobility period compared with the control. Furthermore, this dose of the extract was found to have comparable potency to imipramine (15 mg/kg) and fluoxetine (20 mg/kg). Thus, the extract of *M. fragrans* is capable to elicit a significant antidepressant-like effect in mice, when assessed by both TST and FST. The antidepressant-like effect of the extract seems to be mediated by interaction with the adrenergic, dopaminergic and serotonergic systems.

### Antidiabetic activity

Macelignan is a natural compound isolated from *M. fragrans*. It enhanced the insulin sensitivity and improved lipid metabolic disorders by activating peroxisome proliferator receptor (PPAR,  $\alpha/\beta$ ) and attenuating endoplasmic

reticulum stress, suggesting that it is an antidiabetic agent for the treatment of type 2 diabetes<sup>(42)</sup>.

### Aphrodisiac activity

In Unani medicine, *M. fragrans* (nutmeg) has been mentioned to be of value in the management of male sexual disorders. In an experimental study, Tajuddin et al. (2005)<sup>(43)</sup> have found that the oral administration of 50% ethanolic extract of nutmeg at 500 mg/kg body weight produces a significant and sustained increase in the sexual activity of normal male rats without any conspicuous adverse effects, which might be attributed to its nerve stimulating property.

### Cytotoxicity

Lee et al. (2005)<sup>(44)</sup> have reported that myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene), a naturally occurring alkyl benzene derivative found in nutmeg induces cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. It was observed that a dose-dependent reduction in cell viability occurred at myristicin concentration  $\geq 0.5$  mM in SK-N-SH cells. The apoptosis triggered by myristicin was accompanied by an accumulation of cytochrome-c and by the activation of caspase-3. Chirathaworn et al. (2007)<sup>(45)</sup> observed that the methanolic extract of *M. fragrans*, even 10  $\mu$ g/ml, induces apoptosis of Jurkat leukemia T cell line through SIRT1 mRNA down regulation.

### Memory enhancing activity

Parle et al. (2004)<sup>(46)</sup> have investigated the effect of *M. fragrans* seeds on learning capabilities and memory level in mice. The learning and memory parameters were assessed using elevated plus-maze and passive-avoidance apparatus. Administration of the n-hexane extract of *M. fragrans* at the lowest dose of 5 mg/kg body weight for 3 successive days significantly improved the learning and memory level of young and aged mice. The extract also reversed scopolamine and diazepam-induced impairment in learning and memory of young mice. The observed memory enhancing effect of *M. fragrans* may be attributed to a variety of properties (individually or in combination) such as antioxidant, antiinflammatory, or perhaps procholinergic activity.

### Antioxidant activity

Murcia et al. (2004)<sup>(47)</sup> have evaluated the antioxidant properties of some spices and compared with those of the common food antioxidants butylated hydroxyanisole (BHA) (E-320), butylated hydroxytoluene (BHT) (E-321) and propyl gallate (E-310). Nutmeg, anise and licorice showed the strongest protection in the deoxyribose assay. Nutmeg, propyl gallate, ginger and licorice improved the

stability of oils (sunflower, corn, and olive) and fats (butter and margarine) against oxidation (110°C). When the Trolox equivalent antioxidant capacity (TEAC) assay was used to provide a ranking order of antioxidant activity, the antioxidant capacity of nutmeg was found to be higher than BHT. Murcia et al. (2004) <sup>(48)</sup> reported that phenylpropanoid compound extracts from nutmeg possessed antioxidant activity. Recently Checker et al. (2008) <sup>(49)</sup> observed that lignans present in aqueous extract of fresh nutmeg mace possess antioxidant, radioprotective and immunomodulatory effects in mammalian cells. High antioxidant activity has been reported in monoterpenoid rich extracts such as terpinene-4-ol, alpha-terpineol and 4-allyl-2,6-dimethoxyphenol in nutmeg seed <sup>(50)</sup>. Yadav and Bhatnagar (2007) <sup>(51)</sup> reported that aril part of *M. fragrans* have significant antioxidant activity due to its ability to inhibit lipid peroxidation and superoxide radical scavenging activity in rat. Pretreatment with *M. fragrans* effectively protects the mice against radiation-induced biochemical alterations as evident by decrease in lipid peroxidation level and acid phosphatase activity and simultaneous increase in hepatic glutathione and alkaline phosphatase activity <sup>(52)</sup>.

### Hepatoprotective activity

Morita et al. (2003) <sup>(53)</sup> have reported that myristicin from *M. fragrans* (nutmeg) possessed most potent hepatoprotective activity to rats with liver damage induced by lipopolysaccharide (LPS) plus D-galactosamine (D-GalN). It was also found that myristicin markedly suppressed LPS/D-GalN-induced enhancement of serum TNF-alpha concentrations and hepatic DNA fragmentation in mice. These findings suggest that the hepatoprotective activity of myristicin may be, at least in part, due to the inhibition of TNF-alpha release from macrophages. Sohn et al. (2008) <sup>(54)</sup> observed that the hepatoprotective effects of macelignan, isolated from *M. fragrans* is related to activation of the mitogen activated protein kinase (MAPK) signaling pathway, especially JNK and c-Jun.

### Pesticidal activity

## Clinical effects

In human, nutmeg intoxication resembles to intoxication due to excessive intake of anticholinergic agents, e.g. profuse sweating, flushed face, delirium, dry throat etc. There is always a Biological Effects of *Myristica fragrans* 27 altered state of mind, e.g. hallucinations, confusion and an impending sense of doom. Clinical symptoms may be contradictory depending on the length of time lapsed after ingesting the toxin. Symptoms also vary according to the dose taken and the variability between different samples of nutmegs. <sup>(55)</sup>

# Aim of the study :

The effect of *Myristica Fragrans* on male infertility .

# Chapter two

## Patients and Methods :

A prospective study of 20 male patients was done in Al-Kadhimya Teaching Hospital during four months (November 2018 – March 2019 ) and data was taken from the patients that included :

The age

Medical diseases

And Seminal fluid analysis before and after the treatment

# Chapter three

## Results

	20-30 years No:22			31-40 years No:19		
	B.treat.	A. treat.	P value	B. treat.	A. treat.	P value
S.Con	7.85	9.25	0.167	7.45	8	0.66
S.Mot	3.375	4.25	0.09	4.125	4.575	0.07
S.Mor	15.4%	16.6%	0.14	15.1%	16.3%	0.48

Table (1) / Age



	1.7-6.85 miu/ml No:20			6.851-12 miu/ml No:21		
	B. treat	A. treat	P value	B. treat	A. treat	P value
<b>S.Con</b>	7.74	9.66	0.04	7.38	7.9	0.075
<b>S.Mot</b>	3.75	4	0.78	4.25	4.45	0.31
<b>S.Mor</b>	15.3%	17.2%	0.18	14.7%	16.9%	0.21

Table (2) / Fsh

	1.1-4 miu/ml No:19			4.1-7 miu/ml No:22		
	B. treat	A. treat	P value	B. treat	A. treat	P value
<b>S.Con</b>	<b>8.04</b>	<b>9.37</b>	<b>0.08</b>	<b>7.05</b>	<b>8.1</b>	<b>0.06</b>
<b>S.Mot</b>	<b>3.4</b>	<b>4</b>	<b>0.21</b>	<b>4</b>	<b>4.45</b>	<b>0.07</b>
<b>S.Mor</b>	<b>14.1%</b>	<b>14.45%</b>	<b>0.85</b>	<b>15.1%</b>	<b>16%</b>	<b>0.36</b>

Table (3 ) / LH

	2.27-6.29 ng/ml No:23			6.3-10.3 ng/ml No:18		
	B. treat	A. treat	P value	B. treat	A. treat	P value
<b>S.Con</b>	7.56	9.125	0.15	7.45	7.9	0.10
<b>S.Mot</b>	3.38	4.2	0.10	4.25	4.51	0.24
<b>S.Mor</b>	14.9%	16.2%	0.13	15 %	15.2%	0.36

Table (4) / Testosterone

	<b>B. treat</b>	<b>A. treat</b>	<b>P value</b>
<b>S.Con</b>	<b>6.35</b>	<b>7.36</b>	<b>0.054</b>
<b>S.Mot</b>	<b>4.50</b>	<b>4.75</b>	<b>0.08</b>
<b>S.Mor</b>	<b>15.4%</b>	<b>16%</b>	<b>0.963</b>

Table (5) / Sfa

# Chapter Four

## Discussion

In our study the age group that improved regarding ( sperm concentration , motility and morphology ) after treatment was between (20-30) years old

In our study the FSH , LH , Testosterone increased after treatment , a study that was carried out Thi-Qar (56) in male rats found out the same result , the hormones increased after treatment because MyristicaFragrans contains elemicine and Myristicin which increase the central catecholamine level which is mediator for maintaining rais in FSH and LH and testosterone . <sup>(57)</sup>

In our study the Seminal fluid analysis regarding ( Concentration , Motility and Morphology ) were improved . a same result was obtained from a French study that showed improvement in the same parameters of seminal fluid analysis and showed increased sexual vigor and performance . <sup>(58)</sup>

## Conclusion :

- 1- Most improved age group was (20-30)
- 2- FSH, LH and testosterone improved
- 3- Parameters of SFA ( conc. , Motility , and morphology ) improved

## References :

- 1- *Fertility: Assessment and Treatment for People with Fertility Problems* (PDF). London: RCOG Press. 2004. ISBN 978-1-900364-97-3. Archived from the original (PDF) on 3 August 2010.
- 2- "WHO | Infertility definitions and terminology"
- 3- "WHO | Infertility definitions and terminology".
- 4- WHO | Infertility definitions and terminology
- 5- Balen AH, Dresner M, Scott EM, Drife JO (2006). "Should obese women with polycystic ovary syndrome receive treatment for infertility?". *BMJ*. **332**(7539): 434–5. doi:10.1136/bmj.332.7539.434. PMC 1382524. PMID 16497735.
- 6- Mishail, A., et al. (2009) *Impact of a second semen analysis on a treatment decision making in the infertile man with varicocele: 1809-1811*
- 7- Unexplained Infertility Background, Tests and Treatment Options Advanced Fertility Center of Chicago
- 8- Altmäe S, Stavreus-Evers A, Ruiz JR, Laanpere M, Syvänen T, Yngve A, Salumets A, Nilsson TK (2010). "Variations in folate pathway genes are associated with unexplained female infertility". *Fertility and Sterility*. **94** (1): 130–137. doi:10.1016/j.fertnstert.2009.02.025. PMID 19324355.
- 9- WHO manual for the standardised investigation and diagnosis of the infertile couple. Cambridge University Press, 2000.
- 10- World Health Organisation. WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th ed. Cambridge: Cambridge University Press; 1999
- 11- Dfdg
- 12- Liu PY, Handelsman DJ. The present and future state of hormonal treatment for male infertility. *Hum Reprod Update* 2003;9: 9–23.
- 13- Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukkou E, Michopoulos J. Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003;80(4):914–20.
- 14- G.R. Dohlea, \*, G.M. Colpib, T.B. Hargreavec, G.K. Pappd, A. Jungwirthe, W. Weidnerf  
The EAU Working Group on Male Infertility, 2005
- 15- ] Silber SJ, Grotjan HE. Microscopic vasectomy reversal 30 years later: a summary of 4010 cases by the same surgeon. *J Androl* 2004; 25(6):845–59.
- 16- Belker AM, Thomas Jr AJ, Fuchs EF, Konnak JW, Sharlip ID. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* 1991;145(3):505–11.
- 17- Tournaye H. Surgical sperm recovery for intracytoplasmic sperm injection: which method is to be preferred? *Hum Reprod* 1999 Sep;14(Suppl 1):71–81.

- 18- Schroeder-Printzen I, Ludwig M, Koehn F, Weidner W. Surgical therapy in infertile men with ejaculatory duct obstruction: technique and outcome of a standardized surgical approach. *Hum Reprod* 2000; 15:1364–8.
- 19- Orwa, C.; Mutua, A.; Kindt, R.; Jamnadass, R. & Simons, A. (2009), "*Myristica fragrans*", *Agroforestry Database: a tree reference and selection guide (version 4.0)*, retrieved 2014-06-07
- 20- Orwa, C.; Mutua, A.; Kindt, R.; Jamnadass, R. & Simons, A. (2009), "*Myristica fragrans*", *Agroforestry Database: a tree reference and selection guide (version 4.0)*, retrieved 2014-06-07
- 21- Smith AC. The americanspecies of the myristicaceae. *Brittonia*1937;2:393-510
- 22- Armstrong JE. Pollination by deceit in nutmeg (*Myristica insipida*, Myristicaceae): floral displays and beetle activity at male and female trees. *Am J Bot* 1997; 84:1266-74
- 23- De M, Krishna De A, Banerjee AB. Antimicrobial screening of some Indian spices. *Phytother Res* 1999;13:616-8
- 24- The Wealth of India. Raw materials. New Delhi: Publications and Information Directorate, CSIR 1995;6(L-M):474-9.
- 25- Anonymous. The Wealth of India. Raw materials. New Delhi: Publications and Information Directorate, CSIR 1995;6(L-M):474-9
- 26- Sonavane GS, Sarveiya VP, Kasture VS, Kasture SB. Anxiogenic activity of *Myristica fragrans* seeds. *Pharmacol Biochem Behav* 2002;71:239-44
- 27- Narasimhan B, Dhake AS. Antibacterial principles from *Myristica fragrans* seeds. *J Med Food* 2006;9:395-9
- 28- .  
Grover JK, Khandkar S, Vats V, Dhunnoo Y, Das D. Pharmacological studies on *Myristica fragrans*—  
antidiarrhoeal, hypnotic, analgesic and hemodynamic (blood pressure) parameters. *Methods Find Exp Clin Pharmacol* 2002;24:675-80
- 29- Jan M, Faqir F, Hamida, Mughal MA. Comparison of effects of extract of *Myristica fragrans* and verapamil on the volume and acidity of carbachol induced gastric secretion in fasting rabbits. *J Ayub Med Coll Abbottabad* 2005;17:69-71
- 30- Anonymous. The Wealth of India. Raw materials. New Delhi: Publications and Information Directorate, CSIR 1995;6(L-M):474-9
- 31- Takikawa A, Abe K, Yamamoto M, Ishimaru S, Yasui M, Okubo Y, Yokoigawa K. Antimicrobial activity of nutmeg against *Escherichia coli* O157. *J Biosci Bioeng* 2002;94:315-20
- 32- Mahady GB, Pendland SL, Stoia A, Hamill FA, Fabricant D, Dietz BM, Chadwick, LR. In vitro susceptibility of *Helicobacter pylori* to botanical extracts used traditionally for the treatment of gastrointestinal disorders. *Phytother Res* 2005;19:988-91



- 33- Rani P, Khullar N. Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant *Salmonella typhi*. *Phytother Res* 2004;18:670-3
- 34- De M, Krishna De A, Banerjee AB. Antimicrobial screening of some Indian spices. *Phytother Res* 1999;13:616-8
- 35- Dorman HJ, Deans SG. Antimicrobial agents from plants: antibacterial activity of plant volatile oils. *J Appl Microbiol* 2000;88:308-16
- 36- Smith-Palmer A, Stewart J, Fyfe L. Antimicrobial properties of plant essential oils and essences against five important food-borne pathogens. *Lett Appl Microbiol* 1998;26:118-22
- 37- Cho JY, Choi GJ, Son SW, Jang KS, Lim HK, Lee SO, Sung ND, Cho KY, Kim JC. Isolation and antifungal activity of lignans from *Myristica fragrans* against various plant pathogenic fungi. *Pest Manag Sci* 2007;63:935-40
- 38- Goncalves JL, Lopes RC, Oliveira DB, Costa SS, Miranda MM, Romanos MT, Santos NS, Wigg MD. In vitro anti-rotavirus activity of some medicinal plants used in Brazil against diarrhoea. *J Ethnopharmacol* 2005;99:403-7
- 39- Ram A, Lauria P, Gupta R, Sharma VN. Hypolipidaemic effect of *Myristica fragrans* fruit extract in rabbits. *J Ethnopharmacol* 1996;55:49-53
- 40- Sharma M, Kumar M. Radioprotection of Swiss albino mice by *Myristica fragrans* houtt. *J Radiat Res (Tokyo)* 2007;48:135-41
- 41- Dhingra D, Sharma A. Antidepressant-like activity of n-hexane extract of nutmeg (*Myristica fragrans*) seeds in mice. *J Med Food* 2006;9:84-9
- 42- Han KL, Choi JS, Lee JY, Song J, Joe MK, Jung MH, Hwang JK. Therapeutic potential of peroxisome proliferator-activated receptor-alpha/gamma dual agonist with alleviation of endoplasmic reticulum stress for the treatment of diabetes. *Diabetes* 2008;57:737-45
- 43- Tajuddin, Ahmad S, Latif A, Qasmi IA, Amin KM. An experimental study of sexual function improving effect of *Myristica fragrans* Houtt. (nutmeg). *BMC Complement Altern Med* 2005;5:16
- 44- Lee BK, Kim JH, Jung JW, Choi JW, Han ES, Lee SH, Ko KH, Ryu JH. Myristicin-induced neurotoxicity in human neuroblastoma SK-N-SH cells. *Toxicol Lett* 2005;157:49-56
- 45- Chirathaworn C, Kongcharoensuntorn W, Dechdougchan T, Lowanitchapat A, Sanguanmoo P, Poovorawan Y. *Myristica fragrans* Houtt. methanolic extract induces apoptosis in a human leukemia cell line through SIRT1 mRNA downregulation. *J Med Assoc Thai* 2007;90:2422-8
- 46- Parle M, Dhingra D, Kulkarni SK. Improvement of mouse memory by *Myristica fragrans* seeds. *J Med Food* 2004;7:157-61

- 47- Murcia MA, Egea I, Romojaro F, Parras P, Jimenez AM, Martinez-Tome M. Antioxidant evaluation in dessert spices compared with common food additives. Influence of irradiation procedure. *J Agric Food Chem* 2004;52:1872-8
- 48- Murcia MA, Egea I, Romojaro F, Parras P, Jimenez AM, Martinez-Tome M. Antioxidant evaluation in dessert spices compared with common food additives. Influence of irradiation procedure. *J Agric Food Chem* 2004;52:1872-8
- 49- Checker R, Chatterjee S, Sharma D, Gupta S, Variyar P, Sharma A, Poduval TB. Immunomodulatory and radioprotective effects of lignans derived from fresh nutmeg mace (*Myristica fragrans*) in mammalian splenocytes. *Int Immunopharmacol* 2008;8:661-9
- 50- Maeda A, Tanimoto S, Abe T, Kazama S, Tanizawa H, Nomura M. Chemical constituents of *Myristica fragrans* Houttuyn seed and their physiological activities. *Yakugaku Zasshi* 2008;128:129-33
- 51- Yadav AS, Bhatnagar D. Modulatory effect of spice extracts on iron-induced lipid peroxidation in rat liver. *Biofactors* 2007;29:147-57
- 52- Sharma A, Mathur R, Dixit VP. Prevention of hypercholesterolemia and atherosclerosis in rabbits after supplementation of *Myristica fragrans* seed extract. *Indian J Physiol Pharmacol* 1995;39:407-10
- 53- Morita T, Jinno K, Kawagishi H, Arimoto Y, Suganuma H, Inakuma T, Sugiyama K. Hepatoprotective effect of myristicin from nutmeg (*Myristica fragrans*) on lipopolysaccharide/d-galactosamine-induced liver injury. *J Agric Food Chem* 2003;51:1560-5
- 54- Sohn JH, Han KL, Kim JH, Rukayadi Y, Hwang JK. Protective effects of macelignan on cisplatin-induced hepatotoxicity is associated with JNK activation. *Biol Pharm Bull* 2008;31:273-7
- 55- Jaiswal P, Kumar P, Singh VK, Singh DK. Enzyme inhibition by molluscicidal components of *Myristica fragrans* Houtt. in the nervous tissue of snail *Lymnaea acuminata*. *Enzyme Research* 2009; doi:10.4061/2010/478746
- 56- Ali Esmail Al Snafi\* and Talib Razaq Museher, Hypnotic , Muscle Relaxant , Anticonvulsant and Endocrine Effects of *Myristica fragrans*. *Thi-Qar Medical Journal (TQMJ): Vol( 2); NO( 1); 2008(18-23)*
- 57- Colln, R.;Brown, G.M. and Vau Loon, G.V. *Clinical neurendocrinology* .Black Scientific Publication 1998. P 43
- 58- E.A. Nantia · P.F. Moundipa · T.K. Monsees · S. Carreau , Medicinal plants as potential male anti-infertility agents: a review , *Androl.* (2009) 19:148-158  
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