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The Potential of A Balinese Traditional Medicine Kelor Leaves *(Moringa oleifera)* For Male Infertility Treatment : A Mini Review

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ABSTRACT

Infertility is one of the causes of reproductive welfare disorders of married couples around the world. One of the causes of infertility at the molecular level is *Oxidative Stress* (OS) because the products of *Reactive Oxygen Species* (ROS), both endogenous and exogenous, exceed the levels of antioxidants in the body. The aims of this review is to find out the potential of traditional medicinal from Bali, Indonesia with local name Kelor *(Moringa oleifera)* leaves in preventing the occurrence of potential infertility in men based on the results of research in vivo using animal trials. The method used by the writer is a literature study.The results of this literature review found that kelor/moringa had a positive effect on sexual behavior, especially an increase in libido. In addition, it has a positive effect on spermatogenesis, the quality of spermatozoa especially increases sperm motility, sperm count/volume, germ cell count, renews endogenous antioxidant enzyme activity, reduces levels of ROS, and provides a protective effect on the testes from damage. *Moringa oleifera* contains many free radical blocking molecules. Some phytochemical test results show that moringa contains powerful antioxidants, including alkaloids, flavonoids, saponins, triterpenoids/steroids, tannins.

Keywords: *Moringa oleifera*, male infertility, antioxidant, oxidative stress.

INTRODUCTION

Living things throughout their lives will be exposed to oxidative stress. Oxidative stress in the body's formed cells can form continuously, and it is part of physiological, metabolism, and biochemical reactions, in addition to being obtained from exogenous factors. Oxidative stress has reactive properties that can cause damage to lipid cell membranes, proteins, and DNA [1,2]. Under certain physiological conditions, all aerobic organisms will have a defense in maintaining a balance between oxidative stress, enzymatic, and non-enzymatic antioxidants. However, if there is an imbalance, oxidative stress can impact of DNA damage and can result in damage to body cells [1–3] . This is the basis for various diseases that can interfere with human health, including disorders of the reproductive system.

Spermatozoa have a DNA structure called Mitochondrial DNA (mtDNA). The complex systems that occur in the mitochondria such as oxidation and reduction reactions make mtDNA very susceptible to exposure to oxidative stress. mtDNA is 10-100 times more susceptible to oxidative stress than nuclear DNA, this is due to the proximity of the mtDNA to ETC *(Electron Transport Chain)* and the relatively low DNA repair mechanism[4,5].Damage to spermatozoa mtDNA will cause disruption of the respiration enzyme coding complex, reduce ATP production, interfere with the spermatogenesis process, increase free radicals that damage the spermatozoa plasma membrane, causing infertility[4–8].

Infertility is a disorder caused by the inability of a sexually active partner to get a pregnancy within 1 year without using contraceptives [9–12]. The frequency of infertility is about 10-15% of couples, and 40% of cases are caused by abnormalities in men [13]. The factors that cause male infertility can be classified into two, which are generally influenced by age, frequency of intercourse, and length of effort, while specific factors are divided into four categories, namely the occurrence of reproductive tract obstruction, inflammation, sexual disorders such as erectile dysfunction, and failure to ejaculate which has the potential to reduce the quality of male sperm production eg, complete blockade of spermatogenesis, low sperm count, poor morphology or function, and abnormal sperm motility[14,15].

One of the causes of infertility at the molecular level is oxidative stress (OS) because the products of reactive oxygen species (ROS), both endogenous and exogenous, exceed the level of antioxidants needed by the body. Endogenous ROS molecules are produced in mitochondria. ROS is usually physiologically produced and used to maintain cellular processes such as sperm maturation, capacity, and sperm-oocyte interaction[16]. Research focusing on improving ROS proves that this class of compounds can interfere with spermatogenesis, spermatozoa motility and spermatozoa morphological abnormalities, decreased spermatozoa concentration, DNA integrity, resulting in sperm function becoming deformed and causing infertility[16,17].

ROS can come from within or from outside the body. Research on the increased production of ROS which affects the proper functioning of the diet process has been investigated and has shown a decrease in the thickness of smooth muscle and the lumen of the dorsal artery of the penis, the number of Leydig cells to spermatogenesis [18,19]. Accumulation of fat which adversely affects the vascular system that disrupts the male reproductive system has been found to involve the molecular transcription factor HIF-1[20].

One of the treatments for mitochondrial damage is the use of antioxidant compounds as a therapy to prevent cell oxidative stress, maintain cellular respiratory activity and mitochondrial energy production [21–23]. The body needs antioxidants that serve to prevent new free radicals, protect cells in the body from attacks of free radicals, ward off free radicals and prevent chain reactions so that greater damage does not occur, and repair cells and tissues damaged by free radical attacks. Most natural sources of antioxidants come from plants that were widely used by ancient people as traditional medicine, one of which is Kelor or Moringa *(Moringa oleifera)* [24].

Moringa contains a lot of free radical blocking molecules [25]. Moringa contains 46 powerful antioxidants, these compounds can work to prevent new free radicals, prevent chain reactions, protect cells in the body from free radical attack so that they can prevent oxidative damage to most biomolecules and provide significant protection against oxidative damage[26,27]. In this review, the scientific literature aimed at

evaluating the activity of Moringa leaves in preventing male infertility uses animal models as a reference for development.

METHODS

This study aims to collect data on the effectiveness of the local Kelor or Moringa *(Moringa oleifera)* plant published locally and internationally during the period between 2010 and 2020. This review discusses the potential of the Moringa plant according to scientific information obtained as medicine in curing or preventing infertility. men on an animal trial scale through publications and theses from various University sources. The internet is also used to collect data or reports published in various international scientific journals via the PubMed search engine and Google Scholar. Medical or biomedical books were also used to help complement this review. A literature search illustrating the use of experimental (in-vivo) animal models [(28)]. Key words used include *Moringa oleifera*, male infertility, antioxidants, oxidative stress.

Briefly, this review summarizes scientific information about the potential of Moringa leaves as traditional medicine ingredients including, scientific name and local name (Source from ITIS Report website with taxonomic serial no: 503874), distribution, bioactive compounds, dosage of extracts, duration of exposure, estimation of parameters, and results of anti-infertility studies. The mechanism of work that may occur in this plant is also described in the discussion section.

RESULT AND DISCUSSION

TAXONOMY AND GENERAL DISTRIBUTION

Moringa oleifera is a plant native to Southeast Asia and is widely grown in tropical and subtropical regions around the world including in Indonesia. In Indonesia, this plant has many local names such as Kelor (Bali), Daun Marunggai (Minang, Sumatra), Limaran (Java), and there are still many local seeds for this plant in large areas in Indonesia. In addition to Indonesia, this plant also has designations in other countries such as Moringa, Horseradish tree, drumstick, tree west Indian Ben (English) [(29)], Sajina (Bangladesh) [(30)], Mrum (Cambodia), Ben aile (Perancis) [(31)], ‘ii h’um (Laos) [(32)], Meringgai, Gemunggai, Kelor (Malaysia) [(32)], and Malunggay (Filipina) [(32)].

Moringa *(M. oleifera)* has the following classification :
Kingdom : Plantae
Divisi : Tracheophyta
Class : Magnoliopsida
Order : Brassicales
Family : Moringaceae
Genus : Moringa
Species : *Moringa oleifera* Lam. (Source : ITIS Report)

The distribution of moringa plants is quite wide and almost widely found in various countries especially in countries with tropical and subtropical regions. The spread of this plant is found in Asia region, Africa, America, and Oceania [(33,34)]. However, the sub-district reports, the influx of this plant in Indonesia was mediated by India at the time of viewing and was widely associated with a strong influence with the influx of Hinduism and Buddhism in Indonesia [(35)]. In addition to being known as a traditional medicinal plant, people also hook this plant with mystical things that are believed to be repellents of fine creatures for newly built houses to be widely used as a means of religious ceremonies, especially by Hindus in Bali Province[(36)].

METABOLITES COMPOUNDS

A plant maintaining its survival by carrying out a series of metabolites that produce primary and secondary metabolites [(37)]. Various studies have stated that secondary metabolites have pharmacological bioactivity. Secondary metabolites can be in the form of phenolic compounds, phenylpropanoids,

saponins, terpenoids, alkaloids, tannins, steroids, and flavonoids [38,39]. There have been many observations of flavonoid compounds in plants related to their effects as antioxidants, antibacterials, anti hyperlipidemia, or anti-hyperglycemia [20].

Based on the results of several phytochemical tests, including using samples of Moringa leaves taken in the North Denpasar, Bali, it is known that Moringa leaf extract is dominated by bioactive ingredients such as alkaloids, flavonoids, saponins, triterpenoids / steroids and tannins[40]. The ability of antioxidants to capture DPPH free radicals with an IC value of 4.33 mg / mL [41]. The sample used from Ende shows that the ethanol extract of Moringa leaves contains flavonoids, phenolics, triterpenoids, steroids, and tannins. The ability of antioxidants to capture DPPH free radicals with an IC value of 4.33 mg / mL [42].

Parts of the Moringa, especially the leaves part have a high antioxidant content. Metabolites of Moringa leaves that have an important role in the action of antioxidants are flavonoids. The possibel of mechanism of Moringa can see in Figure 1. Some of the main bioactive phenolic compounds of the flavonoid group such as quercetin, kaempferol, and others[39]. Quercetin is a strong antioxidant with an ability 4-5 times higher than vitamin C and E as a potential antioxidant developed as a medicinal ingredient [42]. Some of the bioactive ingredients can see in Table 1.

Table 1. Secondary metabolites, classes, and role/function of Moringa *(M.oleifera)*

No.	Secondary metabolites	Classes	Role/Function	References
1.	Alkaloid	-Morphine -Quinine -Ephedrine -Strychnine -Nicotine	Alkaloids are one of the important chemical compounds as a source of discovery of new drugs and this compound is widely developed as herbal medicine one of which is cancer because it has antiproliferative properties and male reproductive problems.	(43,44)
2.	Flavonoid	-Flavones -Flavonols -Isoflavones -Chalcones -Flavonols -Anthocyanins	Flavonoids are exogenous antioxidants that have been shown to prevent cell damage due to oxidative stress. The direct or indirect mechanism of the action of flavonoids is signaled to have antioxidant potential. The direct function of flavonoids is to donate hydrogen ions so that they can neutralize the adverse effects of a free radicals and can stimulate the formation of systematic antioxidants marker such as SOD, catalase (CAT), and glutathione peroxidase.	(45–48)
3.	Saponin	-Triterpenoid saponin -Steroid saponin -Alkaloid saponin	Saponins have medical properties that depend on their chemical structure. Saponin compounds have antioxidant effects by forming hydroperoxide as a secondary antioxidant to inhibit the formation of lipid peroxide.	(46,49)
4.	Tannin	-Gallotannins -Ellagitannins -Complex tannins -Condensed tannins	Tannin which functions as an antioxidant, tannin compounds are composed of polyphenol compounds which have free radical scavenging activity, but if the concentration of tannins is excessive, they can have an	(50)

				effect as peroxidant, tannins can degrade DNA and contribute to the formation of hydroxyl radicals	

ANIMAL STUDIES

Several studies have reported the potential of Moringa leaves as anti-infertility tested in animals (animal trials) in vivo. Recent research reported the effect of giving ethanol extract of *M.oleifera* leaves to fertility hormones and cement quality in male albino mice. The administration of the extract is carried out orally for 30 days at doses of 100, 200, and 400 mg/kg. The results stated that the administration of Moringa leaf extract at different doses was able to increase weight, the weight of sexual organs, serum testosterone, Follicle-stimulating hormone (FSH), and Luteinizing hormone (LH) when compared to the control group [(51)]. Similar research was also conducted by Fatoba et al. [(52)] which utilizes Moringa root extract against the sperm production of albino mice. The dose of treatment given is 5, 10, 15, and 20 mL orally for 10 days. The results showed that Moringa root water extract was able to support spermatogenesis and produce good sperm quality.

Moringa leaf extract (MO) is also reported to have radioprotective properties against mobile phone-induced electromagnetic exposure in mice. The experiment was conducted by dividing the test mice into four groups, namely, group I (control) given standard feed, II (200 mg/kg mo leaf extract), III (exposure to 900 RF/MW MHz Field continuously for one hour daily and for 7 days a week), and group IV (exposure to cell phone electromagnetic radiation and MO extract). The results reported the supplementation of MO can regenerate the activity of antioxidant enzymes, lower ROS levels, and increase the activity of *Proliferating cell nuclear antigens* (PCNA) that have an important role in aspects of DNA replication and processes related to replication, bypass, replication due to induction, inappropriate repair of DNA, and chromatin assembly[(53)]. These results confirm that MO extract has the potential as a radioprotective that can damage the quality of sperm indicated by the increase in mouse sperm parameters[(54)]. The results of research on the potential of Moringa leaf extract are presented in Table 2 below.

Table 2. Study of the potential of Moringa under animal studies *(M. oleifera)*

No	Research and References	Animal subject	Dose and duration	Results	References
1	Effects of Moringa oleifera Lam. (Moringaceae) on the reproduction of male mice (Mus musculus)	Twenty- four male mice aged 8 weeks, body weight 28 - 32 g	The treatment rats were given hexane extract of Moringa oleifera leaves at doses of 0.5, 5 and 50 mg / 30 g BW for 21 days.	The results hexane fraction obtained from the leaves of M. oleifera enhances seminiferous tubule, epididymis, testis and seminal vesicle.	(55)
2	Moringa oleifera Leaves Sources of the Mineral Zinc (Zn) to Increase the Libido and Semen Quality of Balinese Bulls	Two males Balinese bulls in healthy condition, 4 - 6 years old, body weight 230-262 kg	Two Balinese cows are kept for three periods. The first period (control), was given feed. The second period was given feed plus 15% of the weight of Moringa oleifera leaf concentrate, and the third period was given food plus Zn. each period for eight weeks.	The results M.oleifera leaves and Zn significantly increase libido, semen volume, total motility and progressive motility of Bali bull sperm. Sperm given Moringa leaves and Zn experience hyperactivity so that it can be predicted that the sperm will be	(56)

3	The Effect of Moringa oleifera Multinutrient Block Of Frozen Semen Quality Balinese Bulls	Five males Balinese bulls, 2-3 years old.	In the treatment group the feed given was a mixture of Moringa leaves, Molasses, salt, minerals, urea and cement as much as 500 grams / day for 6 weeks.	The results Giving Moringa oleifera multinutrient block feed can improve the quality of frozen semen of Balinese bulls.	(57)
4	Ameliorative Effect of *Moringa oleifera* (drumstick) Leaf Extracts on Chromium-Induced Testicular Toxicity in Rat Testes	Forty male Wistar rats (Rattus norvegicus), six weeks old, weighing about 190-200g	Forty male Wistar rats were divided into four groups, mice were given either 150pp mg / kg potassium dichromate or 60 mg / kg body / weight Moringa oleifera extract (MoE) or a combination, for 100 days.	The results of Moringa leaf extract can improve the sperm of mice treated with chromium and Moringa leaf extract.	(58)
5	Effect of Aqueous Extract of Moringa oleifera Seed on Sexual Activity of Male Albino Rats	Healthy male albino rats	The treatment group received suspension of aqueous seed extract of M. oleifera orally at the doses of 1000, 2000 and 5000 mg/kg daily for 7 days respectively.	The results oral administration of aqueous extract moringa oleifera significantly increased the libido and sperm count in experimental animal.	(59)
6	Effect of *Moringa oleifera* leaf powder on sperm count, histology of testis and epididymis of hyperglycaemic mice *Mus musculus*	Three month old Male Swiss Albino mice (Body weight: 25 ± 5 g)	Mice were divided into 3 groups, group I was given normal feed + moringa leaf meal 200 mg / kg bw, group II was hyperglycemic, group III hyperglycemic + moringa leaf meal 200 mg / kg bw for 21 days	The results in the treatment group (group III) there was a significant increase in sperm count, increased sperm motility and decreased spermatozoa mortality	(60)
7	Effects Of Methanolic Extract Of *Moringa oleifera* Leaves On Semen and Biochemical Parameters In Cryptorchid Rats	Twenty male albino rats (200-250g)	The treatment group was given methanol extract of moringa oleifera 200 mg / kg BW for 2 weeks, then cryptorchid was carried out on day 15	The results Methanolic Extract Of Moringa Oleifera Leaves significantly increased sperm count, germ cell count, testicular SOD and total protein in the cryptorchid rats.	(61)
8	Sperm abnormalities induced by pre pubertal exposure to cyclophosphamide are effectively mitigated by Moringa oleifera leaf extract	Two week old male Swiss albino mice	mice intraperitoneally injected with phosphate buffered saline, 50 mg kg^{-1} of cyclophosphamide (CP) and 25 mg kg^{-1} of Moringa oleifera leaf extract (MOE). In combination treatment, mice were injected	The results combining MOE with CP increased the sperm density, motility and reduced head defect and DNA damage. Administration of MOE prior to CP significantly elevated the level of	(62)

			with 25 mg kg^{-1} of MOE 24 h prior to CP injection, 24 h prior and post-CP injection and 24 h post-CP injection for 5 consecutive days (10 mg kg^{-1}) for Six weeks.	superoxide dismutase and catalase with concomitant decrease in lipid peroxidation in the testicular tissue.	
9	The radioprotective effects of Moringa oleifera against mobile phone electromagnetic radiation-induced infertility in rats	Sixty, two- month-old male Sprague-Dawley rats, weighing 150-180 g	The rats were divided into four groups. group I (control) received only standard food. Group II was given a supplement of 200 mg / kg of MO leaf extract daily and for eight weeks with. To III affected group 900 MHz RF / MW field continuously for one hour every day and for 7 days a week. Group IV exposed to cell phone electromagnetic radiation and receive Moringa Oleifera extract.	The results Moringa Oleifera extract renewed the activities of the anti- oxidant enzymes, downregulated the levels of ROS and increased PCNA activity in the testis of electromagnetic radiation exposed serta improvement in sperm parameters of rats	(54)
10	Effects of Increasing Aqueous Root Extract of *Moringa oleifera* on Sperm Production of Albino Rats	Twenty- five (25) adult albino rats with body weight ranging from 200g to 250g	Rats were divided into 5 groups, group I control, group II, III, IV and V were given aqueous extract of Moringa oleifera root 5, 10, 15 and 20 ml orally for 10 days	The results the aqueous extract of Moringa oleifera root extract significant enhanced spermatogenesis and sperm quality	(52)
11	Effect of ethanol extract of Moringa oleifera seeds on fertility hormone and sperm quality of male Albino Rats	Twenty four (24) male Albino Rats	The treated rats were given ethanol extract of M. oleifera seeds at a dose of 100, 200 and 400 mg / kg orally for 30 days	The results the ethanol extract of moringa oleifera increases body weight and sexual organ weight, increases serum testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and improves semen characteristics.	(51)
12	Effect of Moringa leaf powder on reproductive hormones and semen quality of New Zealand White (NZW) rabbits	Thirty-two (32) rabbits	Rabbits differentiated by a ratio of 50:50 were grouped into 4 treatment groups with a dosage of Moringa powder 0.5.10, and 15 g / kg mixed in pellets for 12 weeks.	Supplementation of Moringa powder through feed has a positive benefit on male and female rabbits fertility, however Moringa powder has varied	(63)

				effects, especially on the hypothaban-pituitary-gonadal axis of male and female animals.	
13	Analyzed the effects of cyclophosphamide (CP) toxicity induced in ethanol extract of Moringa (MOE) on the testes of mice	Adult Swiss albino rat aged 8 weeks.	Swiss albino mice were injected with CP (100 mg/kg, one dose a week for 3 weeks) and MOE (100 mg/kg, 5 doses a week for 4 weeks) either alone or with the combination intraperitoneally. Day 35 after initial CP injection, sperm quality, reproductive hormone, and gene expression related to Sertoli and spermatogonial cells.	Giving MOE was able to reduce CP-induced testicular damage by increasing blood parameters, intra-testicular milieu hormone, and modulating gene expression related to Sertoli and spermatogonial cells.	(64)
14	Investigating the efficiency of the ethanolic extract of *M.oleifera* leaves (MLEE) in increasing the physiological response and semen quality of rabbit feces under summer heat stress	Twenty eight (28) adult V-line rabbits	A total of 28 adult rabbits were randomly distributed among the four experimental group. Group I (control) : water, the other three groups : MLEE at doses of 50 (M50), 100 (M100), and 150 (M150) mg / kg BW every day for 12 weeks during summer.	MLEE has a unique phytochemical combination that improves heat tolerance and semen properties of rabbit feces when used at doses of 50 mg / kg BW and for a wide range of ambient temperatures between 28°C and 32°C.	(65)

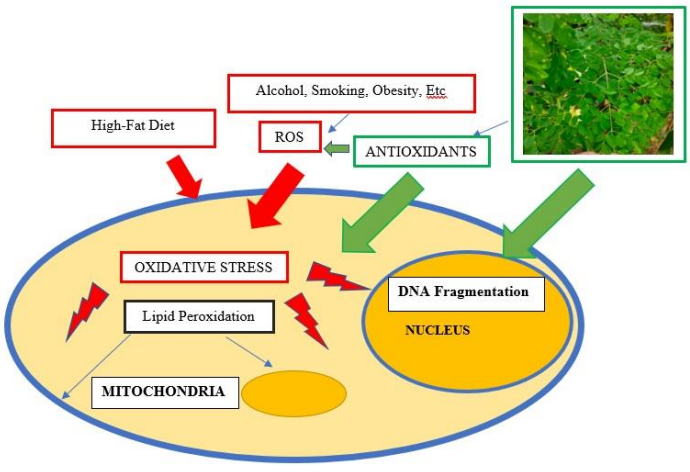

Figure 1. Possible mechanism of antioxidant from Moringa leave in sperm cell (red : negative effect, green : positive effect) (Source adapted & modified from Benatta et al [66])

Figure 1. Possible mechanism of antioxidant from Moringa leave in sperm cell (red : negative effect, green : positive effect) (Source adapted & modified from Benatta et al [66])

CONCLUSION

One of the causes of infertility at the molecular level is oxidative stress (OS) because the products of reactive oxygen species (ROS), both endogenous and exogenous, exceed antioxidant levels in the body. Moringa oleifera contains many free radical blocking molecules. Several phytochemical test results show that Moringa contains strong antioxidants, including alkaloids, flavonoids, quercetin, saponins, triterpenoids/steroids, tannins, zeatin, vitamin C, beta-carotene, selenium, and polyphenols. this compound can protect the body from the bad effects of free radicals. The antioxidants present in Moringa leaves work to neutralize free radicals thereby preventing oxidative damage to most biomolecules and providing significant protection against oxidative damage. The results of this literature review found that moringa had a positive effect on sexual behavior, especially an increase in libido. In addition, it has a positive effect on spermatogenesis, the quality of spermatozoa especially increases sperm motility, sperm count/volume, germ cell count, renews endogenous antioxidant enzyme activity, reduces levels of ROS, and provides a protective effect on the testes from damage.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ETHICAL CLEARANCE

Ethical clearance was not obtained to review this article because it did not involve participants, humans, or experimental animals.

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