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

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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 effect as peroxidant, tannins can degrade DNA and contribute to the formation of hydroxyl radicals	50

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].

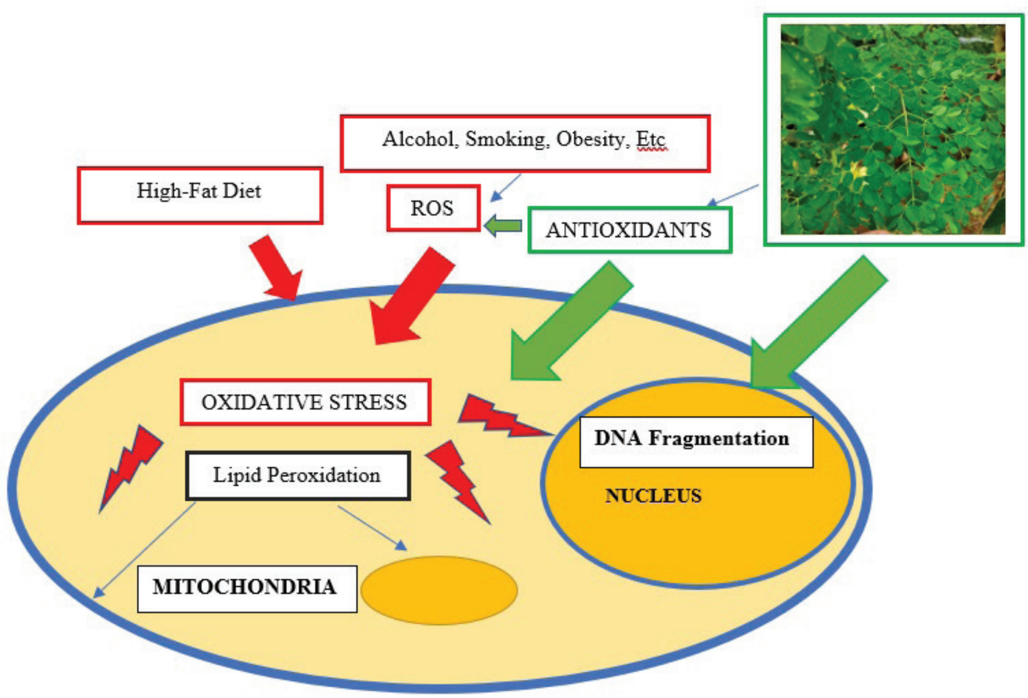

Figure 1. Possible mechanism of antioxidant from Moringa leave in sperm cell (red : negative effect, green : positive effect) (Source adapted & modified from Benatta et al [55])

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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