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The Effect of Anethum Graveolens on Male Fertility: Systematic Review and Meta-Analysis

Seid Mohammed, Birhane Alem Berihu* and Tekleberhan Beyene
Department of Anatomy and Histology, Institute of Biomedical Sciences, College of Health Sciences, Mekelle University, Mekelle- Ethiopia (mseid64@yahoo.com, *birhane.alem@mu.edu.et, teklitina@gmail.com).

ABSTRACT

The literature survey has reported that Anethum graveolens extract is inescapably linked with fertility. Recent studies showed that the aqueous extract of Anethum graveolens extract has an adverse effect on male fertility by affecting serum testosterone level, sperm concentration as well as sperm motility. However, its evidence has not been established. The present paper tries to determine the level of evidence for the effect of dill (Anethum graveolens) on male fertility. MEDLINE, Cochrane Library, PubMed, Academic Search Complete, SPORT Discus, Science Direct, Scopus, Web of Science, and Google Scholar were searched to retrieve the literature used for this review. Keywords utilized across the database search were dill, Anethum graveolens, mice, male fertility, randomized control trial, and experimental. The search was limited to studies in animals; published in the English language. Meta-analysis was conducted to examine the effect of Anethum graveolens (dill) extract administration on male fertility. The overall methodological quality of evidence was assessed using the Pedro scale. Out of 25 studies, four trials met the inclusion criteria for this review. All the studies were included in the meta-analysis. Of these, four studies were included for the analysis of sperm concentration, three studies for sperm motility, and two studies for serum testosterone hormone levels. The meta-analysis results suggested there were no significant differences between male fertility and other interventions in the effects of inducing male infertility. The number of studies regarding the current topic is scarce. The overall quality of evidence was very low. Therefore, it is difficult to conclude whether the aqueous extract of dill seed has or has no adverse effect on male fertility. Considering our meta-analysis, we recommended that there is a need for further investigation to provide adequate evidence for the effect of dill (Anethum graveolens) on male fertility.

Keywords: Anethum graveolens, Dill, Male fertility, Randomized control trial, Quesi experiment.

1. INTRODUCTION

The plant anethum graveolens is useful medicinal plant belonging to family Umbelliferae and is a strong-smelling fennel-like, annual plant reaching a height of about four feet (Monsefi et al., 2014). Ethno medical value of Anethum graveolens is tremendous in traditional medicine as different parts of the plant have been used as antibacterial, antioxidant, anti-hypercholesterolemia, and cancer chemo preventive effects. Additionally, in folk medicine, it is commonly used to improve gastric irritation, indigestion, stomachache, insomnia, and colic (Hosseinzadeh et al., 2002). Studies reported that the Anethum graveolens seed aqueous extracts decreases sexual potency and

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spermatogenesis in males (Weiss and Meuss, 2001; Duke, 2002). High doses of Anethum graveolens seed aqueous and ethanol extracts caused the significant increase in duration of the estrous cycle, diestrus phase and progesterone concentration (Monsefi et al., 2006a; Monsefi et al., 2006b). Utilization of the Anethum graveolens increases milk production and promotes menstruation (Weiss and Meuss, 2001).The Anethum graveolens leaf is used as food flavoring and aroma (de Carvalho and da Fonseca, 2006; Jana and Shekhawat, 2011). The Anethum graveolens seed stimulated progesterone secretion and affect menstrual cycle (Monsefi et al., 2006a,b). It is undeniable that the increase of the population in the developing countries is an anxiety, therefore finding safe and effective family planning involving male can be very useful. Lack of male involvement may be due to in part to the limited contraceptive choice that they have (Mahmood and Ringheim, 1996). So, it requires more research to develop new methods for them. Thus, several medicinal herbs have tested on animal models. Therefore, traditionally plants have been used to control fertility (Mahmood and Ringheim, 1996). Recent studies suggest that Anethum graveolens extract has the anti-fertility effect on the Male Reproductive Functions (Khouri and El-Akawi, 2005; Sailani and Moeini, 2007). In contrast, some research suggests that Anethum graveolens extract enhances the aphrodisiac activity and is not harmful to sperm and male reproductive organs (Madhukar and Rajender, 2009).

Prior to the present systematic review, there was no systematic review conducted to identify the level of evidence on the effect of the Anethum graveolens on the male reproductive functions. It is reasonable to pool investigations to establish evidence on the effect of the Anethum graveolens on the male reproductive functions. Therefore, the objective of this systematic review and meta-analysis was to determine the level of evidence for the effect of dill (Anethum graveolens) on male fertility.

2. METHODS

2.1. Protocol and Registration

Protocol followed as per the Cochrane guidelines and conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Deeks et al., 2008).

2.2. Data Sources and Search Strategy

This review was conducted according to the Cochrane guidelines and has been presented based on the preferred reporting items for systematic reviews and meta-analyses checklist. Mendeley, Cochrane Library, PubMed, Academic Search Complete, Science Direct, and Google Scholar were searched to retrieve the papers for this review. Keywords utilized across database search were Anethum graveolens, male fertility, mice, randomized control trial, and experimental study. As subject headings varied between the databases, various combinations of these keywords were used. The search was limited to the studies in an animal, published in the English language. A search of bibliographies of acquired studies was also performed. Authors have independently conducted the database searches. In addition, four relevant journals (Fig 1) and reference lists of included studies were manually searched. The database searching was performed since September 2017.

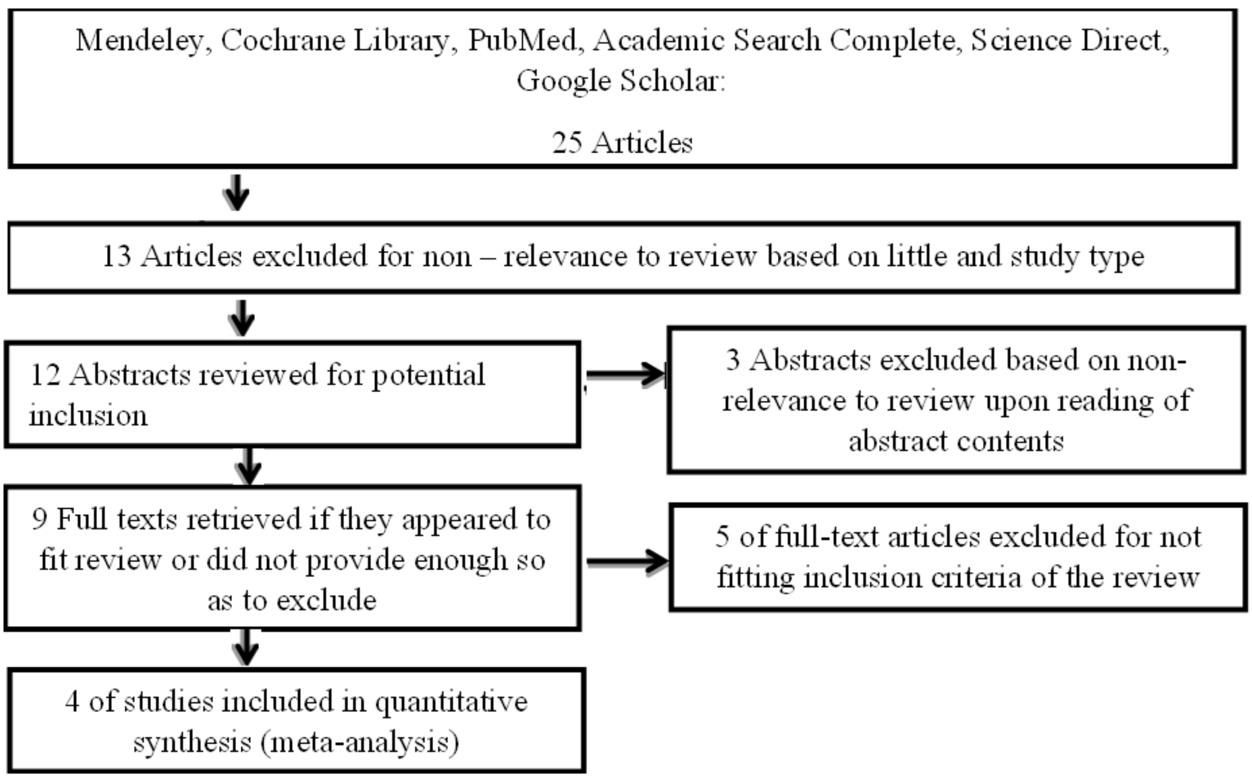

Figure 1.The process of study selection according to the PRISMA flow diagram.

2.3. Types of Studies

To retrieve the papers for this review, studies using the randomized controlled trials (RCTs) and quasi experimental study were included in this study. Only articles published in the English language limited to animal studies were included in this study. For the present review, the focus is being about the effect on male fertility (effect on sperm Concentration, sperm motility, and testosterone hormone level). Research articles conducted on animals using extracts in addition to Anethum graveolens extract were included. Brief trial reports, abstracts, and proceedings from the conference were excluded from the study.

2.4. Intervention

The intervention of interest was the effect of the Anethum graveolens extract on sperm concentration, sperm motility, and testosterone hormone. Studies with Anethum graveolens administration did as the only intervention or with other interventions were included if the same other interventions were applied in the control group. If the exclusive effect of Anethum graveolens extract administration could not be defined in studies involving multiple interventions, those were excluded from the study.

2.5. Comparison

Control groups included no treatment or any form of intervention.

2.6. Outcome Measures

Assessment of sperm concentration, sperm motility, and other testosterone abnormalities were the main outcome measures. Studies showing abnormalities as at least one of outcome measures were included.

2.7. Data Extraction

Authors have independently reviewed all articles for eligibility (Fig 1). For conducting the meta-analysis, outcome data were assessed for eligibility, and scores were extracted from relevant included studies. Data was extracted from the included studies (Table 1) with the standardized form and checked the data to ensure accuracy. Any disagreements regarding the study inclusion of two reviewers were resolved through discussion. The following were recorded from each trial where available: Intervention characteristics (Anethum graveolens extract dose, control condition, and additional treatments); participant characteristics (sex , age, and weight); study characteristics (author and publication year); outcomes (time of outcome assessment and unit of outcome assessment); and evaluation of each domain of the Cochrane risk of bias assessment tool (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting) (Deeks et al., 2008). The outcome was decreased sperm concentration, sperm motility diminished and decreased testosterone hormone level.

Table 1. Characteristics of the included studies.

Study	***Study design***	***Intervention***	***Outcome measure***	***Reported results***
(Shojaee, Ghasemi et al., 2014)	Randomized control trial	Anethum graveolens seeds extract	The effects of Anethumgraveolens L. on the reproductive system of male rat and CREM gene expression in testis of the rat.	Anethum graveolens has specific inhibitory effects on sperm parameters and reproductive functions of male rats, which is probably performed by a reduction of the level of CREM expression.
(Maliheza man and Sara, 2007)	Quasi-experimental study	Anethum graveolens seeds extract	The infertility effect of Anethumgraveolens	The administration of Anethum graveolens seeds aqueous extract did not have antifertility effects in adult male rats.
(Azarpoor and Sarami, 2013)	Randomized control trial	Anethum graveolens leaf extract	the effects of Anethum graveolens juice (PJ) consumption on sperm quality, spermatogenic cell density, antioxidant activity and testosterone level of male healthy rats	Anethum graveolens increase in epididymal sperm concentration, sperm motility, spermatogenic cell density and diameter of seminiferous tubules and germinal cell layer thickness, and it decreased abnormal sperm rate
(Iamsaard, Prabsattroo et al., 2013)	Randomized control trial	Anethum graveolens extracts	effect of Anethumgraveolens extracts on the mounting frequency, histology of testis and epididymis, and sperm physiology	Anethum graveolens significantly increased the mounting frequency, at testis of the mice treated with Anethum graveolens showed high levels of phosphorylated protein. Anethum graveolens extract did not affect the sperm concentration, acrosome reaction, and histological structures of testis and epididymis.

2.8. Assessment of Methodological Quality and Risk of Bias

Authors have used the PEDro Scale to assesses 11 items related to the study internal validity and statistical reporting, except for the first one (eligibility criteria), which is not computed in the total score. Each item is scored as either present (1) or absent (0), leading to a maximum score up to 10. As shown in table two the methodological quality of the included studies was assessed using the PEDro scale. A study with the score of 6 or above was considered of high quality (Herd and Meserve 2008) whereas that with the score of 5 or below was noted as low quality. The risk of bias in the included studies was assessed using 7 criteria recommended by the Cochrane Collaboration (Higgins et al., 2011). The results of assessing the risk of bias were planned a priori to be used in evaluating the quality of evidence and in sensitivity analysis where appropriate.

2.9. Data Analysis

A standard mean difference (SMD) with 95% confidence interval (CI) was an effective measure used for the outcome. A weighted mean difference (WMD) with 95% CI was used to synthesize the level of sperm concentration, sperm motility, and testosterone. The data synthesis has been done with an intention to treat basis. The random effect model was used throughout the review for calculating WMDs and SMDs. The inconsistency of data was examined by looking at the graphical display of the results and by using an I^2. The I^2 is provided with the forest plots as a useful estimate of heterogeneity. As recommended, an I^2 of 50 % or more indicates high inconsistency of data (Deeks et al., 2008). Meta-analyses were conducted to examine the effects of Anethum graveolens extract on sperm concentration, sperm motility, and testosterone level in comparison with control groups. Publication bias was assessed by graphically examining the symmetry of a funnel plot. Review Manager 5.3 was used for all analyses and generating the funnel plot. The forest plot is a figure that appears in the Results section of a systematic literature review. It's a graphic representation of the findings of multiple studies that investigated the same scientific question and measured the same outcome. Funnel plots are a visual tool for investigating publication and other bias in meta-analysis. They are simple scatterplots of the treatment effects estimated from individual studies (horizontal axis) against a measure of study size (vertical axis).

3. RESULTS

3.1. Type of Studies and Their Characteristics

The process of the selecting studies to be included in this meta-analysis and systematic review is illustrated in figure 1. Four articles from a total of 25 records were included in this systematic review. The characteristics of the included studies are presented in table 1. Three studies were RCTs, and one study was Quesi experimental published in the English language.

3.2. Interventions

Variety in comparison interventions was shown in the present meta-analysis. These included effects of both daily administrations of Anethum graveolens seeds and leaf extract on male rats.

3.3. Primary Outcomes

Studies analyzed in this review revealed that dill (Anethum graveolens) shows no significant effect on sperm concentration, sperm motility, and testosterone level.

Table 2. Pedro Scale Criteria.

Authors of study	***Pedro scale criteria***											***Pedro***
	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	
(Shojaee, Ghasemi et al. 2014)		Y	Y	N	N	Y	N	Y	N	Y	N	5
(Malihezaman and Sara 2007)		N	N	Y	N	Y	N	Y	N	Y	N	4
(Azarpoor and Sarami 2013)		Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
(Iamsaard, Prabsattroo et al. 2013)		Y	Y	N	Y	Y	N	Y	N	Y	N	6

Note: Y: Criteria met. N: Criteria not met.

1. eligibility criteria were specified
2. subjects were randomly allocated to groups
3. the allocation was concealed
4. the groups were similar at baseline
5. there was blinding of all subjects
6. there was blinding of all administration who administered the intervention
7. Assessors blinding.
8. Adequate data collection.
9. Intention to treat analysis
10. Between-group statistical comparison
11. Point measures and measures of validity.

3.4. Methodological Quality and Risk of Bias

The results for Pedro score of each study are presented in table 2. The scores ranged from 4 to 9. Two studies were considered of low quality (Shojaee et al., 2014; Malihezaman and Sara, 2007) while other two studies of high quality (Iamsaard et al., 2013; Azarpoor and Sarami, 2013). Three criteria which were eligibility criteria were specified, Intention to treat analysis, point measures and measures of validity were unsatisfied in all studies. Figure 2 shows the summary of assessing the risk of bias. Studies successfully perform low risk of selection bias, allocation concealments, blinding of participants, personnel, and performance bias. There was risk of reporting bias, attrition bias, and detection bias across the included studies.

3.5. Publication Bias

It was difficult to determine if there was publication bias from the funnel plot because of the small numbers of studies (Fig 3).

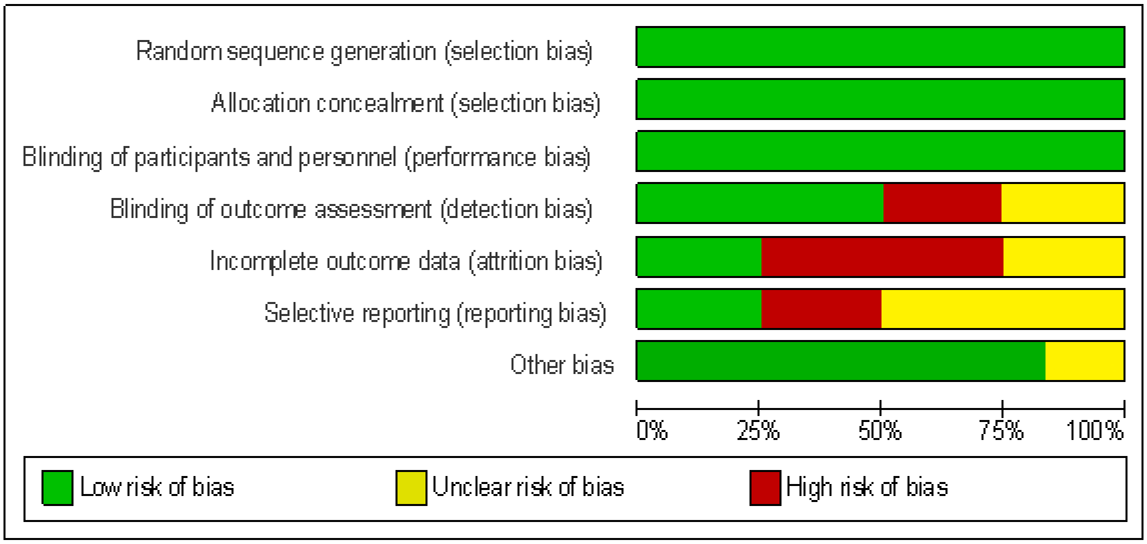

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

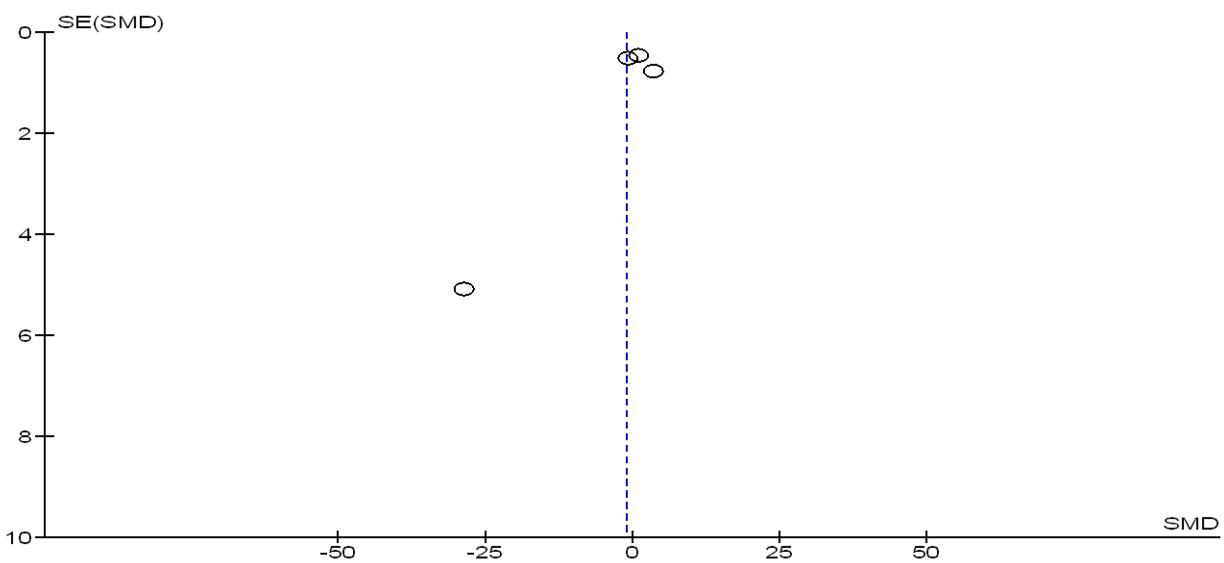

Figure 3. Funnel plot of comparison: Effect of the Anethumgraveolens seed extract on sperm concentration.

3.6. Effect of the Dill (Anethum Graveolens) on Male Fertility

Four different studies were considered for this meta-analysis (Shojaee et al., 2014; Malihezaman and Sara, 2007; Azarpoor and Sarami, 2013; Iamsaard et al., 2013). As heterogeneity was evidenced in all meta-analyses (heterogeneity: τ =8.63; $\chi 2$ = 55.4, df = 3 (P <0.00001); I^2 =95%), (Fig 2), the random effect model was used, and it generated the weights from inverse-variance weighting. In terms of the effects of dill (Anethum graveolens **)** on sperm concentration in comparison with the control group, four studies were identified (Malihezaman and Sara, 2007; Azarpoor and Sarami, 2013; Iamsaard et al., 2013; Shojaee et al., 2014). The overall estimate of the effect on sperm concentration suggested that there was no significant difference between exposed and control group for the reduction of sperm concentration (SMD: -1.13, 95% CI: -4.38-2.13, P: 0.50) (Fig 4). Similarly, the overall estimate of the effect on sperm motility suggested that there was no significant difference between exposed and control group for the reduction of sperm motility (SMD: -0.80, 95% CI: -1.64-0.03, P: 0.06) (Fig 5).

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Azarpoor A. 2013	31.47	1.11	10	67.49	1.29	10	8.0%	-28.67 [-38.62, -18.72]
Shojaee P. 2014	217.89	2.23	8	219.67	2.45	8	31.0%	-0.72 [-1.74, 0.30]
Lamsaard et al 2013	39	9.56	10	30	8.46	10	31.2%	0.95 [0.02, 1.89]
Monsefi M. 2007	6.26	0.16	10	3.91	0.85	10	29.8%	3.68 [2.13, 5.23]
Total (95% CI)			**38**			**38**	**100.0%**	**-1.13 [-4.38, 2.13]**

Heterogeneity: Tau² = 8.63; Chi² = 55.41, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.68 (P = 0.50)

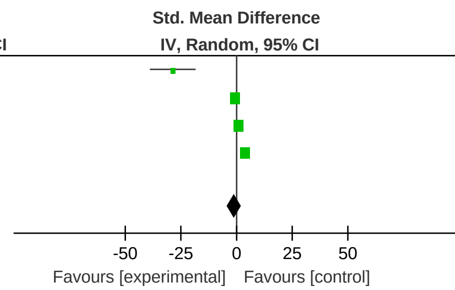

Figure 4. Forest plot of comparison: Effect of the Anethumgraveolens seed extract on sperm concentration.

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**Year**
Monsefi 2007	78.78	1.88	10	78.33	3.8	10	91.0%	0.14 [-0.73, 1.02]	2007
Azarpoor 2013	27.7	1.31	10	55.39	2.17	10	2.6%	-14.80 [-19.99, -9.60]	2013
Shojaeeb P. 2014	64.63	1.32	8	75.32	1.07	10	6.4%	-8.59 [-11.89, -5.28]	2014
Total (95% CI)			**28**			**30**	**100.0%**	**-0.80 [-1.64, 0.03]**	

Heterogeneity: Chi² = 53.66, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.88 (P = 0.06)

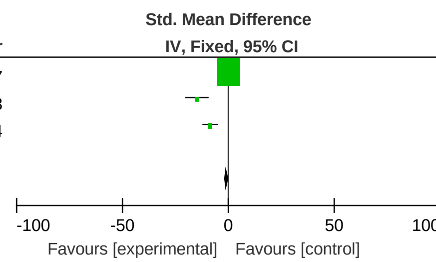

Figure 5. Forest plot: Effect of the Anethumgraveolens seed extract on sperm motility.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Monsefi 2007	3.38	1.14	10	2.41	0.9	10	51.2%	0.90 [-0.03, 1.84]
Shojaee P. 2014	0.689	0.032	8	0.823	0.076	8	48.8%	-2.17 [-3.48, -0.86]
Total (95% CI)			**18**			**18**	**100.0%**	**-0.60 [-3.61, 2.42]**

Heterogeneity: Tau² = 4.40; Chi² = 14.11, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 0.39 (P = 0.70)

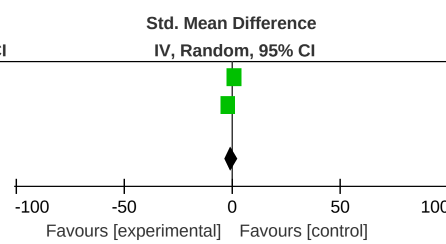

Figure 6. Forest plot of comparison: Effect of the Anethumgraveolens seed extract on serum testosterone hormone level.

The overall estimate of the effect on serum testosterone level suggested that there was no significant difference between exposed and control group for the reduction of testosterone level (SMD: -.60, 95% CI: -0.61-2.42, P: 0.70) (Fig 6). The overall quality of evidence was very low (table 2). Therefore, it is difficult to conclude whether the aqueous extract of dill has or no effect on male fertility.

4. DISCUSSION

This systematic review and meta-analysis were conducted to determine the level of evidence for the effect of the extract of the dill (Anethum graveolens) on male reproductive function. The results of the meta-analysis suggest that there is very low-quality evidence of no difference in the effect of the extract of the dill (Anethum graveolens) on male fertility as compared to control group. On the other hand, the results of each study separately suggest that the extract of the dill (Anethum graveolens) has shown antifertility effect (Cruz-Casallas et al., 2005; Khouri and El-Akawi, 2005; Sailani and Moeini, 2007), although no significant difference is shown when analyzed based on reproductive parameters such as sperm concentration, sperm motility, and serum testosterone level. As the number of studies included in the analyses is very small (n =4), it is reasonable to think that these slightly conflicting results might show scarcity of studies regarding the effects of Anethum graveolens on male fertility in demonstrating actual effects.

Two studies included in this meta-analysis (Shojaee et al., 2014; Azarpoor and Sarami, 2013) have demonstrated that the administration of Anethum graveolensto male mice induces reduction in the concentration of sperm in the center of seminiferous tubules. Shojaee et al. (2014) have reported that there was a reduction in the diameter of seminiferous tubules following administration of the Anethum graveolens. Viable sperm is an essential component of any successful reproduction and the success of reproduction process is dependent on a supply of high-quality gametes (Cruz-Casallas et al., 2005). Approximately 50% of infertility issues are attributable to malefactors. A number of different factors may result in similar reductions of sperm count or motility and affect sperm morphology (Madhukar and Rajender, 2009). One study on the administration of aqueous extract of Anethum graveolens showed a significant reduction in the number and motility of sperm (Sailani and Moeini, 2007), this may be due to the influence of the extract on the cell cycle, cell division and expression of genes necessary for the spermatogenesis. It is also possible that these changes might be a result of changes in the microenvironment of epididymis and creation of a toxic microenvironment presence in Anethum graveolens seed extract, thus influencing sperm count and motility (Shojaee et al., 2014). It could also infer that the treatment may act directly or indirectly on the pituitary gland secretary function causing to a decrease in the androgen (Sailani and Moeini, 2007). It has been demonstrated that the process of spermatogenesis and the accessory reproductive organs functions are androgen dependent (Khouri and El-Akawi, 2005). Therefore, any changes in the androgen production would reflect and explain the decrease in the number of sperms (Sailani and Moeini, 2007). At present, there are no truly dependable criteria for estimating sperm quality. In human, mammals, and fish, the length of time and intensity of spermatozoa motility, the percentage motile sperm and sperm density are all parameters that have been measured in an attempt to assess sperm quality (Billard and Cosson, 1992). Moreover fertilizing capacity is the most conclusive way of testing sperm quality (Billard et al., 1995). Spermatozoa motility is the most commonly used criterion to evaluate semen quality (Bozkurt et al., 2006).

However, spermatozoa motility varies in rigor and duration not only among male but also within an individual male depending on the ripeness, age and time of sampling. The highest motility of the spermatozoa is observed at the peak of the breeding season (Terner, 1986). In many species, sperm is stored to maintain a uniformly high sperm count even with a high ejaculatory frequency. In man, there is no storage, so sperm count is essentially a reflection of production rate, albeit modified by abstinence period. This difference between humans and other animals might sound incidental, but it is fundamentally important with regard to fertility (Sharpe, 2003).

A study done on Ruta graveolens which is a similar species with Anethum graveolens revealed that this medicinal plant significantly reduces sperm concentration (Sailani and Moeini, 2007). Modern experiments have shown some effects exerted by Ruta graveolens on male reproductive system and spermatozoa. A two-month oral administration of Ruta graveolens aqueous extract in male albino rats suppressed Testosterone levels, decreased sexual and aggressive behaviors, reduced sperm motility and count (Khouri and El-Akawi, 2005). Sperm count reductions due to Ruta graveolens have been reported in other studies (Sailani and Moeini, 2007). Naghibi et al. (2010) have previously reported the immediate immobilizing effect of the Ruta graveolens aqueous extract on human spermatozoa in vitro conditions (Harat et al., 2008). The similar pattern has also been reported by other members of the family Rutacea (Gijon et al., 1995; Clarke et al., 2006; Harat et al., 2008).

Studies demonstrated that administration of Anethum graveolens extract showed a reduction in testosterone hormone (Shojaee et al., 2014). Testosterone is synthesized from cholesterol in the Leydig cells. The secretion of testosterone is under the control of LH and the mechanism by which LH stimulates the Leydig cells involves the increased formation of cyclic AMP via the serpentine LH receptor. Testosterone exerts an inhibitory feedback effect on pituitary LH secretion (Matthiesson et al., 2006). It appears that reduction in testosterone level causes a reduction in the inhibitory action of testosterone on LH secretion, thus the secretion of LH increase. Along with testosterone, FSH is responsible for the maintenance of gametogenesis. FSH acts on the Sertoli cells to facilitate the spermatogenesis (Matthiesson et al., 2006).

Based on the studies, Anethum graveolens extract has anti-fertility effect on the male reproductive functions, in contrast, our meta-analysis suggested that no statistical differences were observed between Anethum graveolens extract administration and male fertility as compared to the control group. There are some issues to be considered in our meta-analyses. Firstly, each study has relatively small sample sizes, resulting in only 76 participants in total whereas 200 subjects are considered as a sparse number in terms of GRADE system (Gould et al., 2012). This might also have impacted on the difference between using absolute values and change scores. This difference suggests that there might be differences in assessment of the effect of the extract of the dill (Anethum graveolens) on male reproductive function and control groups at baseline. However, such difference was not statistically different due to wide standard deviation caused by a small number of participants. Secondly, the results are based on studies with low methodological quality, which may cause some biases.

Thirdly, the research design varies between studies and the three studies included were of randomized control trial (Shojaee et al. 2014; Iamsaard et al., 2013; Azarpoor and Sarami, 2013) and one study was quesi experimental (Malihezaman and Sara, 2007). Two out of four studies demonstrated the short-term effects (acute and sub-acute effect) of the treatment of extract of the dill (Anethum graveolens) intervention (Iamsaard et al., 2013; Malihezaman and Sara, 2007) while two studies investigated the effect of the extract of the dill (Anethum graveolens) administration for seven weeks and eight weeks (Shojaee et al., 2014; Azarpoor and Sarami, 2013). Fourthly, the duration of clinical symptoms was unclear in all the four studies. Finally, the long-term effect Anethum graveolens administration is unknown in addition to the exclusion of the non- English articles; therefore, language bias may not be ruled out. These factors could result significant influence on the results of this review. These limitations and the above-mentioned factors could make the validity of current results suspicious.

5. CONCLUSIONS AND RECOMMENDATIONS

The amounts of studies concerning the current topic are scarce. In addition, most of the included studies were considered of low methodological quality. These could lead to overestimating or underestimating the effect of Anethum graveolens administration on male fertility. Therefore, strong recommendations can't be made for the effect of Anethum graveolens extract on male fertility. To provide the evidence-based anti-fertility effect of the Anethum graveolens extract, more research, especially high qualities randomized control trials, regarding the current topic are needed. Also, it is important to set a valid demonstration, including acute, sub-acute, sub chronic, chronic investigation and employ both non-specific and specific determinations where feasible.

Abbreviations

AG: Anethum graveolens; RCTs :Randomized controlled trials; CREM: Testicular responsive element modulator ; PJ : (Punica granatum) graveolens juice; SMD: Standard mean difference; CI: Confidence interval; WMD: Weighted mean difference; DF: Degree of freedom; AMP: Adenosine mono phosphate molecule; LH: Luteinizing hormone; FSH: Follicular stimulating hormone; PEDro: The Physiotherapy Evidence Database

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7. CONFLICT OF INTERESTS

No conflict of interests.

8. REFERENCE

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