



SPERMATOGENIC SYNERGY OF *PHYLLANTHUS EMBLICA* L.: A REVIEW

ADARSH T¹, CHANDRAN AS^{2*}, MURALIDHARAN K³ AND KUMARI S⁴

1: M.D(Ayu), Department of Rasayana Evam Vajikarana (Rejuvenative medicine, Gerontology, Andrology & Epigenetics))

2: Department of Swasthavritta (Community Medicine), KAHER's Shri B. M Kankanawadi Ayurveda Mahavidyalaya, Karnataka, India

3: Department of Rasayana Evam Vajikarana (Rejuvenative medicine, Gerontology, Andrology & Epigenetics)), KAHER's Shri B. M Kankanawadi Ayurveda Mahavidyalaya, Karnataka, India

4: Department of Kayachikitsa (General medicine), KAHER's Shri B. M Kankanawadi Ayurveda Mahavidyalaya, Karnataka, India

***Corresponding Author: Dr. Amal S Chandran: E Mail: dr.amal1409@gmail.com**

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ABSTRACT

Infertility is a threat that is challenging the humanity in the contemporary world. Modern science has developed various artificial reproductive techniques which simulates the natural reproductive physiology. But these techniques are having very limited success rates. Hence it is very crucial to integrate the ancient wisdom which is having solution for all the modern lifestyle disorders. *Phyllanthus emblica* L. (Indian gooseberry) is an ayurvedic traditional fruit which was explained to be enhancing the spermatogenesis in males according to Ayurveda, Traditional Indian system of Medicine. This article emphasises on exploring the therapeutic potential of multiple chemicals which initiates various phytochemical pathways that collectively enhances the spermatogenic potential of this drug. A detailed review was conducted on Scopus, PubMed, Google scholar, Ayush Portal and DHARA. The study involves enlisting of all the active phytochemicals of *Phyllanthus emblica* L. with the help of Dr. Duke's phytochemical database. These phytochemicals are then critically analysed to explore all the possible pathways of chemical reactions which can enhance the spermatogenic activity in human beings. It was found that *Phyllanthus emblica* forms a source for twelve phytochemicals which collectively work as a synergy to enhance the spermatogenic function in males. This research hence substantiates the spermatogenic potential of *Phyllanthus emblica* as explained in Ayurvedic classics.

Keywords: *Amalaki, Ayurveda, Infertility, Medicine, Traditional, Vajikarana*

1. INTRODUCTION

Ayurveda is a traditional Indian medical system emerged in India, 4000 years ago [1]. Ayurveda mainly deals with the octad of treatment (*Ashtangas*), namely *Kayachikitsa* (General medicine), *Balaroga* (Paediatrics), *Grahachikitsa* (Clinical microbiology & Clinical Psychology), *Shalakyatantra* (Eye, ENT & Oro dentistry), *Shalyatantra* (Surgery), *Agadatantra* (Clinical Toxicology), *Rasayana* (Rejuvenative medicine & Gerontology) and *Vajikarana tantra* (Andrology & Epigenetics). Among this, *Vajikarana* is a branch which mainly deals with enhancement of vigour, vitality and libido and promoting the sexual pleasure experienced during intercourse [2]. This branch is further bifurcated into two main categories namely Spermatogenic (*Vrushya*) and Aphrodisiac (*Vajikarana*) [3].

Infertility is a major challenge of the modern era affecting 8-10 percentage of the couples around the globe. As per WHO, in developing countries one out of four couples suffer from infertility [4]. Out of which 20-30 percentage is due to male infertility [5]. Hence it is very crucial to deeply understand the potential of ayurvedic medicines in a way where modern science can complement this ancient wisdom and can collectively work upon curing infertility naturally and scientifically.

Phyllanthus Emblica L. (P.E) is an ayurvedic drug which is having multiple

therapeutic benefits and is also indicated to cure infertility and sexual dysfunctions as per Ayurvedic classics [6, 7, 8, 9, 10]. It was also found to be clinically efficacious in the management of Oligospermia [11]. But limited studies have been done to determine the exact mode of action of P.E in testis with regards to spermatogenesis.

2. REVIEW METHODS

2.1. Inspecting previous research works

To acknowledge the previous reviews done on P.E, we performed a systematic review of peer-reviewed articles published between January 2011 - 2021 in PubMed, Google scholar, Ayush Portal and DHARA. For this we used the keywords like “*Phyllanthus Emblica*”, “*Emblica Officinalis*”, “*Emblica*” and “*Amalaki*”. We have found that PubMed index has published 203 articles with “*Emblica*” in title, out of which, 141 were published in the last 10-year time period. We could find 24 Clinical Trials, 20 Randomized Controlled Trials and 27 review articles when the above filters were applied. Out of which, only 3 systemic reviews were done, which were conducted exclusively on animals while we could not find any Meta-Analysis published so far. It is also to be noted that we did not find any publications emphasizing the spermatogenic property of P.E.

2.2. Enlisting relevant phytochemicals

Dr. Duke's phytochemical database was used as a reliable source to list out the phytochemicals in P.E. However, only those phytochemicals which are found to be having protective as well as enhancing action on spermatogenesis are taken into consideration while finalising the list [12].

2.3. Determining the chemical pathways

The phytochemicals enlisted are further explored to establish the probable pathways or chemical reactions which can improve the spermatogenic potential. These pathways are relevant enough to form a blueprint of overall drug action of these phytochemicals. Each phytochemical is searched with keywords such as "stimulate", "activates", "modulates", "regulates" and "initiates". And hence we came to understand the pathways in which these chemicals are acting as a stimulant.

These pathways or chemical reaction are then searched with keywords such as "semen", "sperm", "testis", "FSH", "LH" and "fertility". These articles are then connected with each other respectively to form a probable network of chemical interactions that can occur in testis. These studies are then considered in framing up this review article forming the final synergy of all possible chemical pathways initiated by P.E.

3. VAJIKARANA TANTRA

Vajikarana tantra is defined as the branch of Ayurveda which specializes in augmenting, refining, revitalising and rehydrating - smidgen, intoxicated, impotent and anhydrous semen respectively [13]. It is gaining popularity in the modern era as humanity is disrupting its own metabolic equilibrium with modern diet and lifestyles. On this regard, we are forced to integrate the ancient therapeutic knowledge and harness the modern interventions with this traditional knowledge.

4. *Phyllanthus emblica* L.

Phyllanthus emblica L. (P.E) is referred as *Amalaki* in ayurvedic contexts which is advised to be consumed on a daily basis (*Nitya Sevana*) [14].

It is classified under *Triphala* (Three fruits) and is also widely used as an antiaging drug (*Vayasthapanam*) in nature [15, 16]. It is also known as Indian gooseberry due to its popularity in our subcontinent. It is a highly potent multi-dimensional therapeutic drug which is found to be acting not only at the systemic level, but also at the molecular level [17].

5. Phytochemicals in *Phyllanthus emblica* L.

We have used Dr. Duke's phytochemical database to determine the chemicals which have enhancing action in spermatogenesis. These phytochemicals along with their activity counts are listed in **Table 1**.

Table 1: phytochemicals along with their activity counts

S. No.	Phytochemicals	Activity count
1	Arginine	14
2	Ascorbic Acid	112
3	Astragalin	7
4	Beta Carotene	53
5	Ellagic Acid	51
6	Linoleic Acid	27
7	Niacin	12
8	Palmitic Acid	13
9	Quercetin	176
10	Rutin	87
11	Selenium	
12	Zinc	

6. SPERMATOGENETIC SYNERGY OF P.E

6.1. Arginine

Arginine one of the key essential compounds for spermatogenesis. Various studies have been done to demonstrate the protective effect of this compound in spermatogenesis [18]. It stimulates sperm motility and was also found to be clinically beneficial in treating asthenozoospermia [19, 20].

It enhances testicular development through Nitric Oxide and Putrescine and also activates glycolysis of spermatozoa [21, 22]. Arginine supplementation significantly improves semen quality, testosterone concentration and testes histological parameters [23].

6.2. Ascorbic acid

Ascorbic acid (Vitamin C) plays a key role in seminal function through its anti-oxidant property. It was found to be directly proportional to sperm quality [24]. It has also exhibited a significant therapeutic effect in improving the fertility of smokers

[25]. Supplementing it in regular diet was found to be showing protective effect in testicles [26, 27].

Ascorbic acid exposure to mesenchymal stem cells were found to be acting as an amplifier in its metabolism [28]. Human testis is also found to be having embryonic stem cells which functionally resembles these mesenchymal stem cells [29]. This in turn opens an area to be researched upon to analyse the action of Ascorbic acid on these stem cells and their probable impact in spermatogenesis.

It is also found to be increasing procollagen messenger RNA in human skin fibroblast [30]. Hence, we can we can debate that it might perform the same action in testis as these procollagens are crucial in achieving spermatogenesis [31].

6.3. Astragalin

Astragalin was also found to be showing protective effect on spermatogenesis [32]. It was found to be regulating and modulation transcription factors (NF- κ B, TNF- α , and TGF- β 1) enzymes (iNOS, COX-2, PGE2,

MMP-1, MMP-3, MIP-1 α , COX-2, PGE-2, HK2, AChE, SOD, DRP-1, DDH, PLC γ 1, and GPX) kinases (JNK, MAPK, Akt, ERK, SAPK, I κ B α , PI3K, and PKC β 2) [33].

Out of these nuclear factor- κ B (NF- κ B) [34] and transforming growth factor beta 1 (TGF- β 1) were found to be acting as a regulator in spermatogenesis and steroidogenesis in Leydig cells [35]. Enzymes such as iNOS [36], MIP-1 α [37], AChE [38], PGE-2 [39], DRP-1 [40] was also found to be modulating steroidogenesis and spermatogenesis in testis.

Out of these Nuclear Factor- κ B (NF- κ B) [41] and Transforming growth factor beta 1 (TGF- β 1) [42] and enzymes such as iNOS [43], MIP-1 α [44], AChE [45], PGE-2 [46], DRP-1 [47] was also found to be modulating steroidogenesis and spermatogenesis independently.

6.4. Beta carotene

Beta Carotene was found to be having a synergy with Vitamin B metabolism to boost the sperm competitiveness [48]. It stimulates the progenitor cells [49] which is an initiating cellular factor for spermatogenesis [50]. It was also proven to show protective effect in titanium [51], methotrexate [52] and acrylonitrile [53] induced testicular toxicities.

6.5 . Ellagic acid

Ellagic acid was found to be acting upon the testis through its protective effect in the body. As per the Chem BL database, it was

found that Ellagic acid is acting upon Aldose reductase receptor in humans. This compound is known to be stimulating spermatogenesis in testis through various metabolic pathways [54].

Ellagic acid increases total antioxidant capacity, eliminating reactive oxygen species, chelating ferrous ions and forming complexes with ions contributing to the reduction to free radical formation by inhibiting the Fenton reaction [55]. It also increases testicular weight, testis volume, spermatocyte, sertoli cells and leydig cells through enhanced gene expression of Bcl2 [56].

Ellagic acid activates AMPK pathway and peroxisome proliferation. AMP activated protein kinase (AMPK) is an enzyme pathway in linking the energy sensing to metabolism [57]. It was found that AMPK is present in several parts of spermatozoa including the sperm heads equatorial segment, the intermediate piece, the midpiece and the flagellum. AMPK pathway plays significant role in regulating the motility and plasma membrane fluidity in sperms [58].

Recent studies that AMPK function in Mammalian spermatozoa plays a key role by signalling kinase in spermatozoa that acts as an essential linker between metabolism energy and sperm ability to fertilize.

Moreover, ellagic was also found to be showing protective effect in testicular

toxicity induced by Arsenic [59], monosodium glutamate and tobacco smoke metabolite-acetic acid [60].

Hence, we conclude that ellagic acid is one of the key phytochemicals which plays a significant role in promoting the testicular function with regards to spermatogenesis and steroidogenesis. It has both antioxidant defence system as well as hormonal axis modulation and protective action against testicular tissue damage.

6.6 Linoleic acid

Linoleic enhances the cellular migration by inducing Mitochondrial Ca^{2+} influx and causes Peroxynitrite generation and Protein Nitrolysis [61]. This further enhances the seminal parameters such as concentration, motility and morphology of sperms since Peroxynitrite formation plays a key role in the mechanism of mitochondrial metabolism in sperms [62]. Conjugated linoleic Acid was also found to be increasing progressive sperm motility [63].

6.7 Niacin

Niacin, a well-known anti-oxidant is found to increase serum testosterone [64]. It activates the G protein oestrogen receptor [65], which plays a key role in regulating pituitary testicular axis and spermatogenesis by modulating gonadotropin releasing hormone [66]. Niacin also activates P13K/Akt Cascade via PKC and EGFR trans activation-dependent pathways through hydroxyl - carboxylic acid receptor

through which plays a crucial role in acrosome reaction [67].

6.8 . Palmitic acid

Palmitic acid improves the functional assay through beta-oxidation metabolic pathway to provide ATP in sperms which further enhances the sperm function [68]. The studies on the metabolism of Palmitic acid in dates back to early 1970s and it was enlisted as one of the key elements in CoASH ligase (AMP) pathway [69, 70].

6.9. Quercetin

Quercetin is another flavonoid compound which is also present in most of the fruits and vegetables. Here, Quercetin acts as an amplifier to enhance the action by regulating AMPK in testicular sertoli cells [71]. We have come into this assumption by exploring the action of Quercetin as a regulator in AMPK pathway as an activator. Meanwhile the same activated AMPK was found to be regulating the gonadal functions in humans [72].

Along with this function, quercetin was also found to be an activator of Ca^{2+} activated K^{+} channels in human umbilical cord [73]. The same action can be expected in the interaction of quercetin on testicular leydig cells in LH/hCG signalling cascade [74].

Hence, the compound quercetin can be taken as a key promoter in testicular function and can be expected to enhance the spermatogenic activity in mates.

6.10. Rutin

Rutin, another polyphenolic compound, has exhibited protective effect in various testicular toxicities [75-78]. It shows anabolic effect in testicular tissues and also modulates testicular functions [79].

6.11. Selenium

Selenium is a key element which supports spermatogenesis by a mechanism involving selenoproteins [76]. It was also found to be densely supplied to the testis disregarding the amount of oral intake [77]. This element was also enlisted as one of the key ingredients for spermatogenesis occurring in other organisms as well [78]. Therapeutic application of this element is also having remarkable outcomes [79].

6.12. Zinc

Zinc is very essential for spermatogenesis and its supplementation is a well-known strategy in the modern era to counter male infertility issues. Zinc was listed as one of the key elements influencing multiple seminal parameters [80] and it was found to be significantly improving semen volume, sperm motility and the percentage of normal sperm morphology [81].

7. DISCUSSION

P.E, as a multi systematic nutraceutical, is having its action in various systemic levels in the body. It was found to be influencing the DNA telomere length as well as the DNA repairs [82]. These explorations justify the potency of this drug in human physiology. When it comes to the field of

male infertility and spermatogenesis, the chemicals which are described above can be considered as the key players in its mode of action. This literature does not point out a single drug - single chemical action. This article emphasizes to show multiple chemicals taking part in the entire mode of action of P.E on spermatogenesis. Henceforth, this highlights the unique synergy of P.E as potent ayurvedic drug to enhance the spermatogenic function. Here we can also see that multiple molecules act through same pathways which subsequently results in the enhanced drug action.

Various attempts have been made to substantiate the clinical efficacy of P.E in male infertility and testicular functions. This article is an initiation step or a referral literature to work upon the pharmacological drug-ligand interactions in humans. This is not a complete study as we need further affirmations for the existence of these drug reactions and pathways. This article can be taken as a blueprint for further articles yet to be published on this context. Hence this literature work directs towards further practical justifications through molecular docking as well as drug-ligand interactions.

8. CONCLUSION

P.E, also known as *amalaki* as per Ayurveda, has underwent critical analysis with regards to its spermatogenic property. This analysis has led to the enlistment of twelve phytochemicals which directly or

indirectly influence the spermatogenic properties. We have emphasised upon multiple chemical pathways that are influenced by P.E which collectively promotes and regulates the spermatogenesis in males. Many of these chemicals are abundantly found in various edible fruits and vegetables, but the combination and synergy are responsible for the elevated drug efficacy of P.E as a spermatogenic natural supplement.

Here we conclude that no single drug can exhibit its mode of action through a single chemical pathway. Various molecular interactions can lead to the collective synergy that results in the final efficacy of the drug administered.

9. LIMITATIONS

Even though the description and pathways of chemical interactions are mentioned. Further researches are needed to substantiate the individual action of these chemicals after administering the drug.

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