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ASSESSMENT OF MOLECULAR ACTIVITY OF *Eranda* (*Ricinus communis* L) IN THE MANAGEMENT OF MALE INFERTILITY WITH NETWORK CONSTRUCTION

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ABSTRACT

Background: Male infertility is one of the rising issues in recent days, due to abnormal lifestyle, genetic causes and drug side effects. The prevalence has increased more than 50% in recent days. On the contrary, conventional medicines that are used in treatment of infertility, are associated with various systematic illness. So, there is a need for development of a drug with safety and efficacy. **Introduction:** *Eranda* (*Ricinus communis L*) is indicated for management of infertility in many classical texts of *Ayurveda.* Efficacy of *Eranda* (*Ricinus communis* L) is already proved by different in-vivo studies. But, understanding the mode of action is still needs to be explored. Present research work is an attempt to unveil the mode of action of Erand in male infertility at molecular level. **Materials & Methods:** Acquired the phytochemicals from plant online databases, checked their drug-likeliness and the Phyto-targets to overlap with the disease targets which gave the common targets of *Eranda (Ricinus communis L)* and Male infertility. With this network was constructed. The phytochemicals and targets which were having higher degree in the Network were assessed for molecular mechanism. **Result:** We found that there were 8 phytochemicals, fifteen pathways and 37 targets which are involved in the network. It is found that CYP1B1 has highest binding affinity for ellagic acid, a phytoconstituent found in *Eranda (Ricinus communis* L). **Conclusion:** The network and the docking results showed the clear picture on the mechanism of molecules of *Eranda* in male infertility. This study opens avenues for future targeted invitro validation of identified pathways, which facilitates development of mechanism-based formulations of *Eranda* in Male infertility

Keywords: Male infertility, *Ricinus communis L,* Network pharmacology, Molecular interaction

INTRODUCTION:

The World Health Organization (WHO) recognizes infertility as a condition in which the sperms are having anyone of these symptoms such as early ejaculation, lower number or absence of sperms, abnormal shape and abnormal motility. Large population surveys estimated that 72.4 million people worldwide suffer from marital infertility, despite the paucity of global prevalence data. Furthermore, according to WHO estimates, in 50% of couple sub-fertility is due to the male component, and 9% of couples globally experience reproductive problems **[1]**. There are various causes of male infertility including obesity, smoking, lifestyle changes, environmental toxins, genetic causes, malignancies and side effects of the medicines. Though there are numerous modern medications such as Tamoxifen, Clomiphene and Aromatose inhibitors they produce side-effects such as nausea, visual disturbances, oedema, skin rashes and even erectile dysfunction **[2]**.

Eranda (*Ricinus communis L* L) is used in *Ayurveda* for managing Male infertility. *Eranda* (*Ricinus communis* L) *moola* is mentioned in *Charaka Samhita* as *Vrshya* & *Vataharanam sreshtam* it told as *Agreya* (best drugs)**[3]**. *Eranda* (*Ricinus communis* L) is having Anti-diabetic, Antioxidant, Neuroprotective, Anti- inflammatory, Analgesic and Spermatogenic activity **[4]**. Though there are plenty of in-vitro and in-vivo studies reported the spermatogenic activity of this plant, but the mechanism of action is not clearly stated. Hence, present study is taken up to analyse the phytochemicals present in the plant *Eranda* (*Ricinus communis* L) followed by construction of the network using the databases, consequently evaluation of the binding affinity of the phytochemical and the disease targets, to understand the mechanism of the plant at molecular level.

MATERIALS & METHODS:

Acquiring Phytochemicals from Different Databases:

Both Dr. Duke's Phytochemical and Ethnobotanical Databases **[5]** and IMPPAT 2.0 (Indian Medicinal Plants, Phytochemistry, and Therapeutics 2.0) **[6]** were used for searching phytochemicals related to *Eranda* (*Ricinus communis* L). The two primary factors used to choose the phytochemicals from these databases were drug likeliness and oral bioavailability. The canonical smiles were then retrieved from the PubChem database. **[7]** The SwissADME database was then used to predict a number of ADME variables. **[8]** Using BindingDB, an online site that analyses similarities and has a similarity score of ≥0.85, the target of the *Eranda*

(*Ricinus communis* L) phytochemicals was determined. **[9]** Following the identification of the disease targets linked to each phytochemical associated with *Eranda* (*Ricinus communis* L), the UniProtKB database was used to standardize the target names **[10]**.

Assessing Target Genes from the Human Protein Atlas (HPA) And Genecards Databases Associated to Male Infertility:

We used the Human Protein Atlas and Gen e Cards database gateways to gather information on therapeutic targets linked to male infertility. using the term "Male infertility" to pinpoint targets **[11, 12]**. Using the Venny 2.1.0 tool, the overlapping disease targets from *Eranda* (*Ricinus communis* L) in male infertility cases were filtered **[13]**.

Construction of the Network:

A Protein-Protein-Interaction network was constructed using STRING version 11.0 in order to comprehend a relationship made up of interconnecting target genes for significant phytochemicals in *Eranda* (*Ricinus communis* L) **[14]**. A medium level of confidence was determined at 0.50 FDR for the species "Homo sapiens," which we chose for reliability validation. Further these gene targets were taken to Cytoscape 3.7.2 for further construction of top 10 targets using Cytohubba, an app that gives data regarding top 10 genes and its calculations **[15]**.

Exploring the KEGG Pathway:

The KEGG (Kyoto Encyclopaedia of Genes and Genomes) analysis was conducted after the species Homo sapiens was selected and the potential targets of the *Eranda* (*Ricinus communis* L) effect on male infertility were put in a STRING database. An overview and selection of the routes were created.

Disease Pathway – Phyto-targets – Disease targets Linkage:

The *Eranda* (*Ricinus communis* L) network was built using Cytoscape 3.7.2 after data regarding active phytochemicals, enriched pathways, and overlapping targets had been exported and processed **[16]**. Using the network analyser, the topological evaluation was conducted. To ascertain the function and connection between the overlapping targets of male infertility and the active phytochemicals, the degree strength of the network was investigated.

Molecular Docking:

From the RCSB PDB and Pub Chem databases, the crystal structures of the top three compounds and the three most significant target proteins were retrieved, respectively **[17]**. The protein structures were stabilized by adding polar connections and removing water molecules using the Biovia DS tool. Auto dock 1.5.7 was used to add Kollmann charges to it **[18]**. The binding interaction between top target proteins and ligands was predicted using the docking technique, and binding sites were automatically identified using PyRx software **[19]**. Using the Biovia Discovery Studio program, the interaction with the best docking scores in two dimensions has been shown **[20]**.

RESULT:

Assessment of the acquired Phytochemicals from Biological Databases:

A total of 66 phytochemicals were obtained from both IMPPAT and Dr. Dukes Phytochemical and Ethnobotanical database after removing the duplicates from both the databases. The Swiss ADME and PubChem databases were used to screen for toxicity and ADME, and 26 phytochemicals were chosen based on their oral absorption, bioavailability and Lipinski violation. We gathered and used the Binding DB and UniprotKB databases to identify 62 target genes in total related to these 10 active phytochemicals.

Analysis of the disease targets:

Curated gene-disease information was extracted from the Gene Cards and HPA databases using the keywords "Male infertility." After removing duplicate genes through a thorough screening method, 6302 genes associated with male infertility were found. The Venny 2.1.0 tool was used to further obtain the overlapped gene by intersecting the genes associated with male infertility and Phyto-targets in *Eranda* (*Ricinus communis L*) - 62. **Figure 1** illustrates the 37 Phyto-targets that were discovered to share similarities between *Eranda* (*Ricinus communis L*) and male infertility.

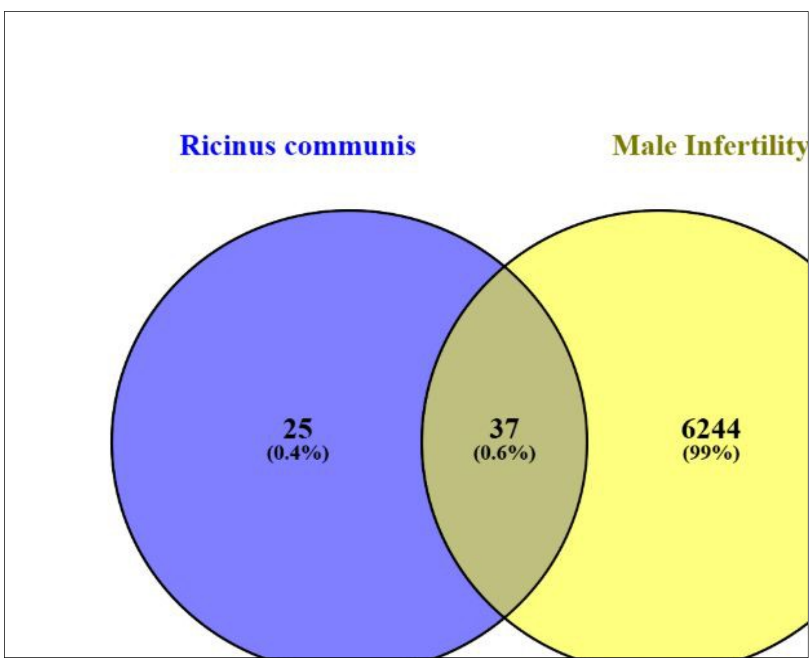

Figure 1: Overlapping targets of *Eranda (Ricinus communis* L*)* and Male infertility

Protein Interaction of the Phyto-Targets, Disease Targets & Phytochemical:

The Protein – protein interaction was made using STRING database with the phytochemicals that are common from Venny 2.1. i.e. 37 targets were imported from STRING database and the PPI was constructed. **Figure 2** illustrates the PPI of *Ricinus communis L.*

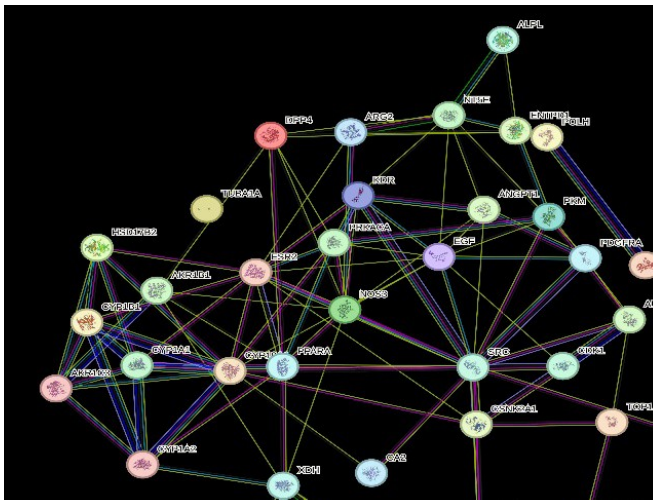

Figure 2: PPI of *Ricinus communis* L.

Top Ten Gene targets:

The top 10 gene targets were acquired from Cytohubba after the construction of PPI Network that is linked to Cytoscape software. The top 10 gene targets were ESR2, EGF, CYP1B1, HSD17B2, KDR, CYP1A1, SRC, AKR1C3, CYP1A2 AND NOS3. CYP1A1, CYP1B1 targets were taken for molecular docking analysis.

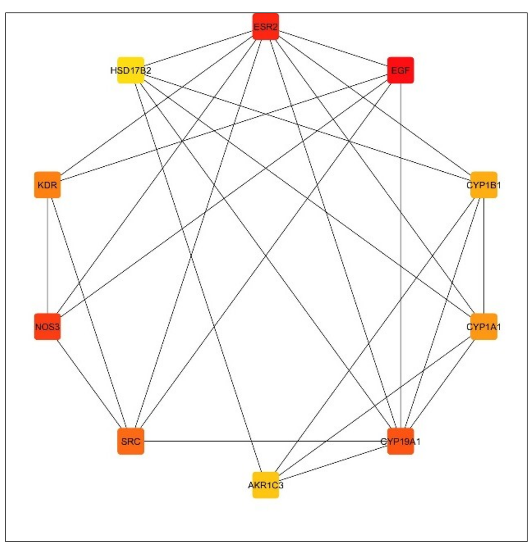

Figure 3: Cytohubba of Top 10 gene targets

Assessment of the Pathways:

To investigate the signalling pathways, KEGG functional enrichment analysis was carried out using the STRING database. To evaluate the mechanism of action of *Eranda (Ricinus communis* L*)* in male infertility, the best 15 pathways out of a total of 37 pathways were selected. **Figure 4** depicts the top 15 pathways in which the targets act on the disease.

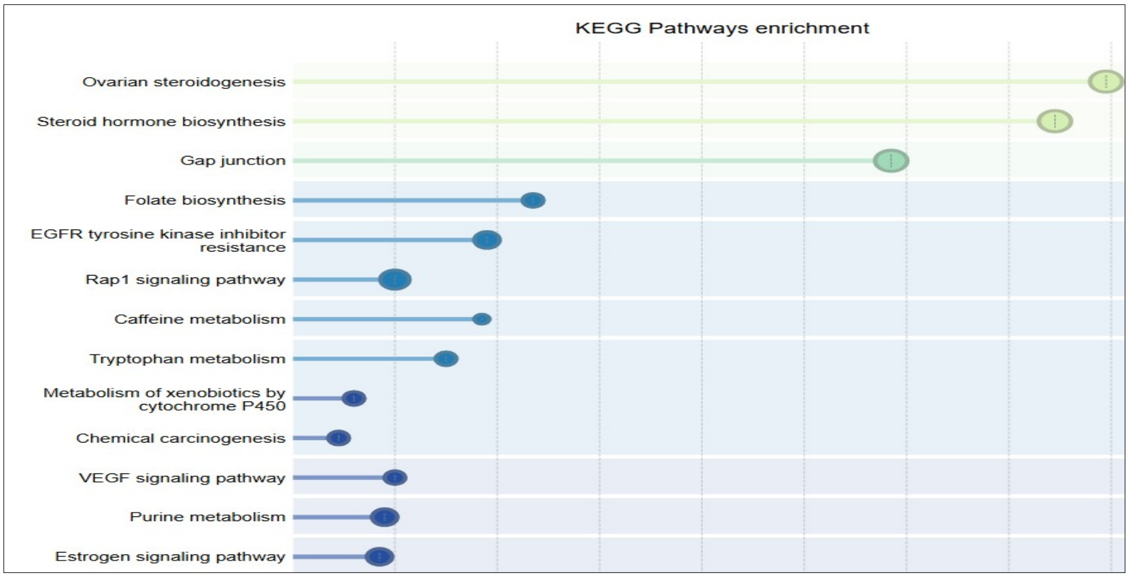

Figure 4: KEGG pathway of overlapping targets and disease

Network Construction:

With a total of eight phytochemicals, fifteen pathways, and thirty targets, the network was constructed using the software Cytoscape 3.7.2 in male infertility. **Figure 5** illustrates the network of *Eranda* (*Ricinus communis* L) phytochemicals, male infertility targets, and disease pathway.

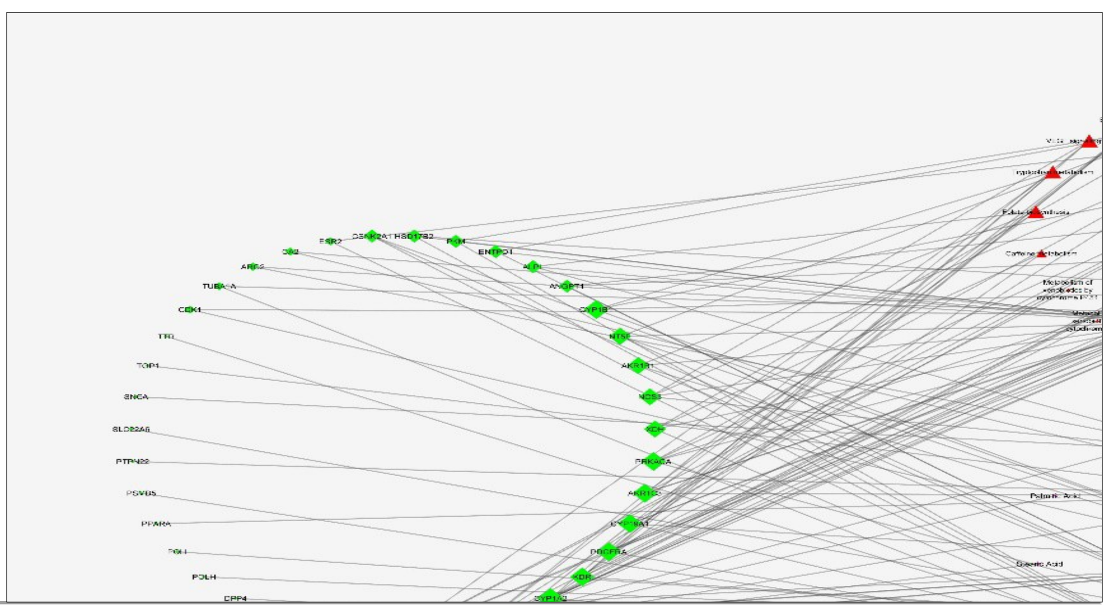

Figure 5: Network (Target-Phytochemicals-Pathway) analysis of *Eranda* (*Ricinus communis* L)

Analysis of Molecular docking:

Using docking of molecules, the validity of the networks relating the three hub targets and bioactive phytochemicals, as well as possible binding processes, have been investigated. Quercetin, Apigenin, and Ellagic acid—three phytochemicals found in *Eranda* (*Ricinus communis L*) exhibited favourable interactions with CYP1A1, CYP1B1, and PDGFRA. Among this Ellagic acid on CYP1B1 showed highest binding affinity. The result of the molecular docking is shown in the **Table 1**. In **Figure 6** the left column depicts the 3-dimensional images of the targets are portrayed while in the right column the binding of the phytochemicals of and the selected disease targets, the first one 6udl is CYP1A1 and to its right is binding of CYP1A1 and Ellagic acid, in the middle row left side the target molecule is PDGFRA (3pmo) and to its right the binding of Ellagic acid and the target. The left side of the last row contains CYP1B1 (6oyu) and to its right is binding of CYP1B1 and Ellagic acid.

Table 1: Molecular docking analysis of *Eranda* (*Ricinus communis L*)

Phytochemical	Binding affinity of targets and Phytochemicals			
	Targets	CYP1A1	PDGFRA	CYP1B1
	PDB ID	(6udl)	(3pmo)	(6oyu)
Quercetin		-10.5	-8.3	-10.6
Apigenin		-10.3	-8	-10.7
Ellagic acid		-10.6	-9.3	-10.8

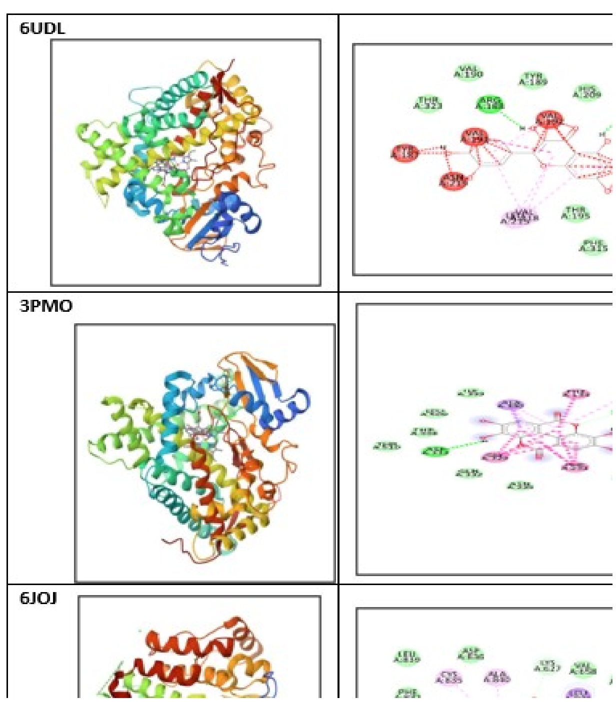

Figure 6: Molecular Docking Analysis of Target and Phytochemicals

DISCUSSION:

Eranda (*Ricinus communis L*) is a plant which is widely available all over India, this plant is extensively used in Indian system of traditional medicine (*Ayurveda*) in various disease such as *Amavata* (Rheumatoid arthritis), *Sandhi vata* (Osteo-arthritis) and it is also indicated as *Vrshya* (boosts vigour) **[21]**. However, there are certain in-vitro researches so as to substantiate the mode of action of *Eranda* (*Ricinus communis L*) in Male infertility. An in-vivo study on analysis of *Eranda* (*Ricinus communis L*) root in male Wistar rats for assessment of spermatogenic activity suggested that the root of *R. communis* increases their serum testosterone levels and several categories of sexual activity (excitation) at the dosage of 20mg/kg. This research indicates that *Eranda (Ricinus communis* L*)* root raises serum testosterone levels to treat sexual dysfunctions brought on by low sperm counts and serum testosterone levels **[22]**. So, on evaluating *Eranda* (*Ricinus communis L*) in Male infertility there were certain Phyto-targets, disease targets, disease pathways and phytochemicals through which *Eranda (Ricinus communis* L*)* works in Male infertility.

CYP1B1 in male infertility:

The cytochrome P450 enzyme family member CYP1B1 contributes to male infertility by its metabolism of a variety of substrates. New research indicates that it also affects male reproductive health. The CYP1B1 role on male infertility are probably through these ways: i) Steroid metabolism: The metabolism of steroids, including testosterone, which is necessary for sperm maturation and production. Variations in CYP1B1 might cause disruptions in steroid metabolism, leading to aberrant sperm parameters and perhaps contribute to infertility **[23]**. ii) Sperm Production and Function: The motility, morphology and sperm count that are essential for a successful fertilization can be impacted by changes in CYP1B1 gene expression or activity. iii) Potential for Therapeutic Targeting: By comprehending the distinct functions of CYP1B1 in male reproductive health, tailored treatments may become possible. The creation of medications that alter CYP1B1 metabolism or activity may enhance sperm characteristics and reproductive results **[24]**.

PDGFRA in male infertility:

Particularly in testicular development and spermatogenesis, PDGFRA is essential for male reproductive health. The testes cell migration, proliferation, and differentiation depend on this receptor tyrosine kinase, which binds to Platelet-Derived Growth Factor (PDGF). Infertility in men can result from PDGFRA signalling disruption **[25]**. PDGFRA is expressed in the developing testis and is essential for Leydig cell differentiation and testicular cord development. Leydig cells need PDGFRA signalling to mature properly because they produce testosterone and INSL3, which are necessary for male sex differentiation and spermatogenesis. During testis development, PDGFRA has a role in the migration and proliferation of Leydig cells as well as the surrounding cells **[26]**. Infertility can result from PDGFRA mutations or aberrant expression, which can interfere with spermatogenesis and testicular development **[27]**.

Quercetin in male infertility:

Quercetin a flavonoid with anti-inflammatory and antioxidant qualities, will help in male fertility by shielding sperm from harm and maybe increasing sperm motility. According to research, it helps by lowering toxic reactive oxygen species (ROS) and protecting sperm antioxidant enzymes from oxidative stress. Furthermore, it may facilitate spermatogenesis, which could have an indirect effect on sperm quality **[28]**. Quercetin has antioxidant properties and it will help in lowering oxidative stress. The motility, viability, and DNA integrity of sperm cells can all be negatively impacted by oxidative stress. Infertility may be exacerbated by quercetin's ability to lessen inflammation in the testes and other reproductive tissues. Sperm motility is important for fertilization and studies have indicated that quercetin can increase sperm motility. Quercetin may also aid in defending sperm DNA against oxidative stress and other harm **[29]**. Quercetin with -10.6 kcal/mol has shown its highest binding affinity towards CYP1B1 and has given a further validation of its role in the disease.

Ellagic acid in male infertility:

Male infertility may be treated using ellagic acid, a polyphenol that is present in vegetables and it is present in *Eranda* (*Ricinus communis* L). Its main advantages come from its anti-inflammatory, anti-apoptotic, and antioxidant qualities, which work together to preserve and improve sperm and testicular function. Eliminating oxidative stress, a significant contributor to sperm failure, is one of ellagic acid's main functions **[30]**. Sperm motility, viability, and DNA integrity are all maintained by this action. By inhibiting pro-inflammatory cytokines and boosting anti-inflammatory signals, it also lessens testicular inflammation, promoting a more favourable environment for spermatogenesis. Additionally, ellagic acid protects against apoptosis, which helps stop germ cells from dying too soon, particularly when exposed to stress or toxins **[31]**. In the docking Ellagic acid has shown binding affinity of -10.8 kcal/mol gives us a clear understanding that the action of this phytochemical in Male infertility plays a vital role.

Metabolic pathway role in male infertility:

During spermatogenesis, metabolic activities that control oxidative equilibrium, hormone synthesis, energy production and cellular integrity are essential for male fertility. High levels of energy are needed by sperm through mitochondrial oxidative phosphorylation and glycolysis. Sertoli cells converts glucose to lactate that is essential for sperm. Diabetes and other disorders that affect glucose metabolism affect sperm quality and energy flow. Metabolic pathways, which are frequently changed in metabolic disorders, also control FSH and testosterone, which are essential for sperm formation. While modest levels of ROS are normal, excessive ROS, which are frequently found in obesity or metabolic syndrome, can harm the DNA and membranes of sperm. DNA repair and membrane integrity are supported by lipid, amino acid, and nucleotide metabolism. The gut microbiome also affects fertility by reducing inflammation and generating healthy metabolites. The understanding of metabolic pathway is essential for treating male infertility. Being one among the top 15 pathways it plays a pivotal role in the disease **[32]**.

With this we can come to an understanding of the mechanism of action of *Eranda* (*Ricinus communis L*) in Male infertility, the molecular docking results also showed us that CYP1B1 showed highest binding affinity on Ellagic acid. The main aim of study in understanding the mechanism and pinpointing the Phytochemicals is completed. Furthermore, investigation is needed on the phytochemical and the target for supplementary validation of this study. This study has some lacuna such as there are only selective database which are taken for assessment of phytochemicals, targets and pathways which may create a bias for this study. This study has given the basic interpretation of *Eranda* (*Ricinus communis L*) action in Male infertility. Further evaluation on the plant is needed to come up with a validation on its safety and efficacy.

CONCLUSION:

The main aim of any system of medicine is to cure the disease and *Ayurveda* mainly uses plant-based medicines in treating various diseases. Though therapeutic action of individual herbs is clearly mentioned in classical texts, in-silico analysis approach as done in this study helps for understanding the mode of action.

Eranda (*Ricinus communis L*) the plant, which is used by various *Ayurvedic* practitioners in the treatment of Male infertility has potential Phyto-targets and phytochemicals that help in the management of Male infertility as explored. Especially CYP1B1 which has highest binding affinity on Ellagic acid is one example. These molecular insights warrant further in vitro validation and promote practice of evidence based therapeutic applications of *Eranda* in Male infertility.

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CONFLICT OF INTEREST: Nil

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ABBREVATIONS:

WHO – World Health Organisation

ADME – Absorption, Distribution, Metabolism and Excretion

SMILIES - Simplified Molecular Input Line Entry System

IMPPAT - Indian Medicinal Plants, Phytochemistry and Therapeutics

PPI – Protein-Protein Interaction

HPA – Human Protein Atlas

STRING – Search Tool for the Retrieval of Interacting Genes

KEGG – Kyoto Encyclopaedia of Genes and Genomes

RCSB - Research Collaboratory for Structural Bioinformatics

PDB – Protein Data Bank

FDR – False Discovery Rate

CYP1A1 - Cytochrome P450 Family 1 Subfamily A Member 1

CYP1B1 - Cytochrome P450 Family 1 Subfamily B Member 1

PDGFRA - Platelet-Derived Growth Factor

Receptor Alpha

ROS – Reactive Oxygen Species

DNA – Deoxyribonucleic acid

FSH – Follicle-Stimulating Hormone