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Review Article

APPLICATIONS OF SYNTHETIC AND HERBAL NANOPARTICLES AS APHRODISIACS: A SYSTEMATIC REVIEW

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ABSTRACT

Men with Erectile Dysfunction (ED) experience difficulty in initiating or sustaining a firm erection during sexual engagement. Pharmacological agents, commonly referred to as aphrodisiacs, effectively treat erectile dysfunction. Aphrodisiac drugs, whether synthetic or herbal, have limited bioavailability, leading to reduced oral absorption. Particle size reduction strategies can address this issue. Nanosize demonstrated a substantial enhancement in oral and transdermal bioavailability when using nanoparticles composed of pure components. The use of nanoparticles at the prescribed dosage is considered safe, and when applied to the skin in a transdermal manner, they do not exhibit any signs of irritation or histopathological alterations, making them suitable for skin application. Furthermore, nanoparticles enable the control, sustenance, and prolongation of drug release.

Keywords: Nanoparticles, Aphrodisiacs, Erectile dysfunction, Bioavailability, Transdermal

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INTRODUCTION

Erectile Dysfunction (ED) is a sexual condition characterized by the inability to achieve or sustain a firm erection during sexual activity [1]. While ED commonly impacts a patient's quality of life, it is important to recognize that it is not solely a physiological ailment. Furthermore, ED is associated with reduced self-esteem and the deterioration of partner relationships [2]. Erectile dysfunction may impact familial discord, a phenomenon that can be influenced by one's age. Aphrodisiacs are medications that can effectively treat erectile dysfunction.

The limited bioavailability of second-generation phosphodiesterase type 5 (PDE-5) inhibitors, such as tadalafil, avanafil, sildenafil, and vardenafil, hinders their oral absorption as aphrodisiac drugs. The medications in question are tadalafil, avanafil, sildenafil, and vardenafil. Tadalafil and avanafil are classified as BCS class II medicines due to their poor solubility and high permeability [1, 3, 4]. Sildenafil exhibits a modest oral bioavailability of approximately 40% [5]. Vardenafil exhibits limited bioavailability and undergoes extensive hepatic first-pass metabolism, resulting in decreased absorption of the drug [6]. Herbal treatments containing icariin, an active chemical found in the genus Epimedium, have low bioavailability. These medicines are used as aphrodisiacs alongside PDE-5 pharmaceuticals. The active ingredient of *Curcuma longa*, curcumin, exhibits limited water solubility, low bioavailability, an unstable structure, and rapid systemic elimination, posing challenges for its application [7-9].

Several strategies, such as solid dispersion, nanoformulation, the prodrug approach, the supercritical liquid method, and other techniques, can address the issues of medication solubility and bioavailability [1]. Nanoparticles can improve the stability and solubility of active compounds by protecting unstable clusters in drugs that are taken by mouth or put on the skin [4, 10, 11]. A number of nanoparticles, including PDE-5 inhibitors, papaverine hydrochloride, sialorphin, nitric oxide, stem cells from adipose tissue, sonic hedgehogs, and extracts of medicinal plants and active compounds, have shown a lot of promise as ways to treat ED [12]. During the fabrication of preparations, researchers can develop diverse techniques for producing nanoparticles.

The application of nanoparticles in both synthetic and natural treatments is extensive, although there remains a lack of comprehensive information regarding the characterization of the resultant nanoparticles. Furthermore, aphrodisiacs can be administered orally or transdermally. This paper looks at previous research to find out what the difference is between nanoparticles with synthetic pharmaceuticals and herbal drugs as aphrodisiacs, taking into account both oral and transdermal administration. Illustrates the systematic review method (fig. 1).

Nanoparticles for drug delivery with aphrodisiac properties

Nanoparticulate drug delivery systems, or NPs, have many benefits because they are small, better soluble, can stick to mucous membranes, deliver drugs more precisely, have dual-release properties, and are more bioavailable. Nanoparticle delivery systems are made up of colloidal mixtures that are very small and can hold medicines that are both water-and fat-loving [13]. Both synthetic and herbal medications used as aphrodisiacs exhibit low solubility, resulting in limited bioavailability. Particle size reduction strategies are employed to enhance the bioavailability of aphrodisiac medications, namely PDE-5 inhibitors like avanafil, tadalafil, sildenafil, and vardenafil. Women utilize flibanserin to augment sexual desire [16]. Nanoparticles, such as nanosponges, solid dispersions, nanospheres, nanocrystals, and Poly Lactic-Co-Glycolic Acid (PLGA) microspheres, have been demonstrated to enhance the bioavailability of both synthetic and natural aphrodisiacs.

Increasing the solubility through the formation of complexes with avanafil nanosponges enhances the bioavailability [4]. The simultaneous impact of both reduced crystallinity and decreased particle size at the nanoscale level can further enhance solubility. While polymers are used to make tadalafil nanocrystals, they might change how well the drug dissolves in water by acting as a solubilizer [15]. Decreasing the particle size of flibanserin enhances its solubility, resulting in a substantial increase relative to pure flibanserin. The increase in particle size reduction leads to a larger contact area between the particle surface and the solvent, hence enhancing solubility [7]. Moreover, polymers can serve as stabilizers by preventing the aggregation and deposition of pharmaceuticals through their absorption on the drug's surface. Additionally, polymers have the ability to establish hydrogen bonds with drugs. Tadalafil exhibits enhanced solubility due to the generation of dispersed molecules and the amorphous structure of a solid [21].

Researchers have found that high water solubility significantly improves the pharmacokinetic characteristics of medicines, such as their bioavailability and therapeutic efficacy. The research [22]

suggests that the solubility of bovine serum albumin-NPs cholecalciferol is fourfold greater than that of pure cholecalciferol. Solid lipid nanoparticles (SLNs) derived from naftopidil offer precise control over drug release. These systems serve as effective carriers for lipophilic pharmaceuticals, enhancing the bioavailability of poorly water-soluble medications by means of nanoparticles. Furthermore, SLNs can serve as a drug delivery system [23].

Reducing particle sizes can enhance the capacity to permeate biological membranes due to the increased surface area of the particles. The size of nanoparticles is crucial in influencing their efficacy in medication delivery [24]. Reducing the size of particles can result in increased and more consistent absorption efficiency. The spherical morphology of the particles facilitates the dispersion of the medication [25]. Non-spherical nanoparticles have distinctive optical properties that can be easily modified by altering their size and form [26]. Eurycomanone nanoparticles facilitate medication penetration through the blood-brain barrier, enhancing their targeted delivery [20]. Nanoparticles of curcumin make it easier for the drug to get deeper into the skin, which leads to better systemic circulation and the physiological effects that follow [8]. Facilitating the absorption of the active compound into the core of nanoparticles and reducing the particle size enhances the bioavailability of icariin, thereby increasing its solubility [7]. Smaller particle size enhances dispersion [27].

By reducing the size of synthetic medications and natural aphrodisiacs with low solubility and bioavailability to the nanoscale, we can create stable formulations that have increased bioavailability. By making particles smaller, the permeability of PDE5 drugs, specifically those in BCS class II, can be raised to the same level as drugs in BCS class I.

An overview of the utilization of drug-loaded nanoparticles in both synthetic and traditional medications for their aphrodisiac properties are reported in table 1.

Characterization of nanoparticles as aphrodisiacs

Researchers synthesize the avanafil nanosponges using the freeze-drying technique, employing cyclodextrins (β-CD and Sulfobutylether-β-CD) and different ratios of crosslinkers (ranging from 1:2 to 1:6). When β-CD crosslinking gets stronger, it gets harder to make complex nanosponges because the drug and the active site of β-CD can't interact as well. The steric action that occurs prevents the creation of complex nanosponges. A larger ratio of nanosponges to pharmaceuticals leads to a decrease in drug loading as a result of increased saturation and repulsive forces. Particles larger than 1000 nm can get trapped in the mucosal surface layer, hindering their absorption. Particle size and zeta potential are determinants that can regulate biological activity, hence influencing bioavailability, metabolism, elimination, and toxicity. The electric charge on the surface of the particle can impact the success of reaching the desired cell. Cellular uptake is enhanced in the particles because the significant surface charge of the cell membrane is a result of their strong binding, which facilitates electrostatic interaction between anionic and cationic nanoparticles [4].

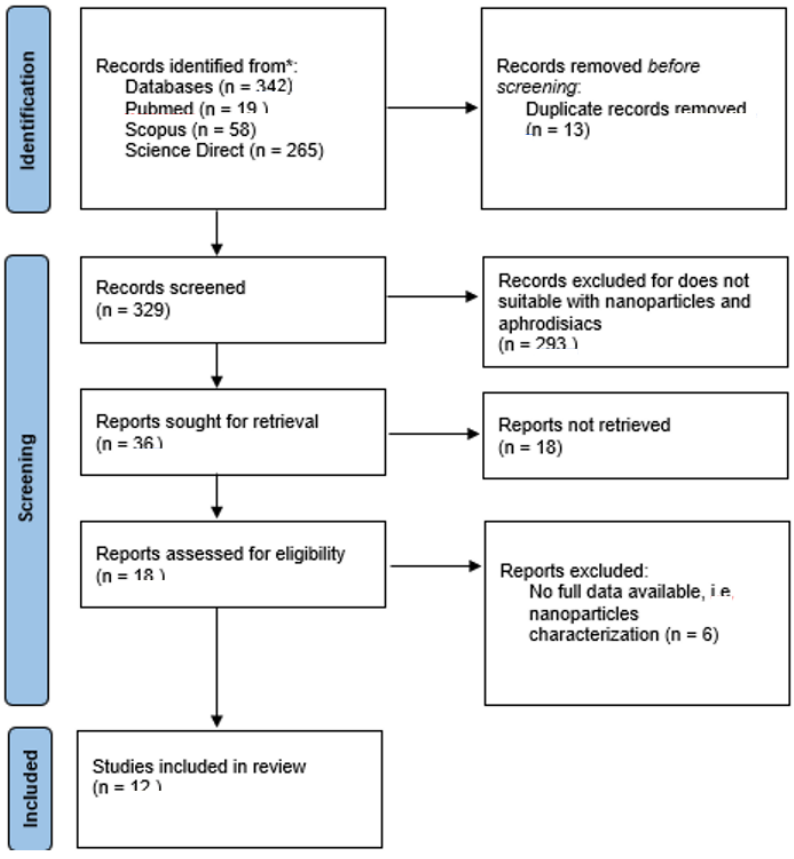

Fig. 1: The PRISMA flow diagram of the study

Hot melt extrusion, spray drying, and solvent evaporation techniques can synthesize tadalafil into amorphous crystals. The spray drying process yields the most diminutive particle size [14]. Temperature influences the particle size of tadalafil, with higher temperatures causing an increase in particle size. This phenomenon occurs because of the reduction in drug solubility at low temperatures, resulting in sluggish particle formation. Additionally, the rate of crystal growth can be influenced by temperature variations [15]. Chitosan can generate nanoparticles, resulting in smaller particle sizes while minimizing the required amount of chitosan. When more tetraethyl orthosilicate and fixed chitosan were added, vardenafil nanoparticles with similar particle sizes were made. A high zeta potential indicates a high level of physical stability [6, 25, 28, 29]. Stability and uniformity are projected to increase with larger magnitudes, regardless of the type of charge [28].

Table 1: Summary of herbal and synthetic nanoparticles as aphrodisiacs

S. No.	Active compound	Nanoparticles used	Production technique	Nanoparticles characterization	Profile	Year	Ref
1	Avanafil	Nanosponges, orally administration at a dose of 20 mg/kg BW of rats	The process of freeze drying was conducted using two types of polysaccharides, namely β-CD and SBE-β-CD, with different ratios of crosslinkers ranging from 1:2 to 1:6.	The particle size is 743±165.46, the polydispersity index (PDI) is 0.19±0.05, the zeta potential is 14.6±3.44, and the loading capacity ranges from 41.62% to 97.66%. There is no focus on the highest points that suggest a decrease in the quality of being crystalline and the creation of both inclusion and non-inclusion complexes. An interaction occurs between nanopsponge and avanafil. Crystals that have a form resembling a needle.	The rate of release is substantially accelerated, resulting in a 2.5-fold increase in oral bioavailability and enhanced effectiveness.	2022	[4]
2	Tadalafil	Solid Dispersion, orally administration (*in vitro* studies)	Spray drying, solvent evaporation method and hot-melt extrusion.	The thermogram displayed distinct tadalafil crystals with a pointed apex and sharp edges. The crystals have a spherical shape and a particle size smaller than 40 μm. The spray drying process achieves the smallest particle size, and there is no chemical interaction between tadalafil and Soluplus.	The dissolving rate has been enhanced, resulting in accelerated drug release during the initial phase followed by a consistent release over time (as observed in an *in vitro* test). The solid dispersion remains stable for a duration of 4 w.	2020	[13]
		Nanocrystal, orally administration at a dose of 2 mg/kg BW of rabbits	Anti-solvent precipitation ultra-sonication method	The particle size ranges from 226.1 to 340.0, with spherical particles that have a soft surface and uniform hue. Partial amorphization leads to the formation of crystalline tadalafil. There are no alterations in the spectra observed on FTIR (Fourier Transform Infrared Spectroscopy).	The saturation solubility has been significantly enhanced, resulting in a 98% increase in the rate of drug release during a 30-minute timeframe. Additionally, there has been an observed rise in mounting frequency, intromission frequency, and ejaculatory latency, as well as an improvement in oral bioavailability.	2021	[14]
		Nanoparticles, orally administration at a dose of 1,8 mg/kg BW of rats	Antisolvent precipitation	The particle size ranges from 193±2.6 to 238±3.2 nm, with a high frequency and rounded shape. The dispersion consists of solid amorphous crystals.	The oral bioavailability is greatly enhanced by employing antisolvent precipitation and spray drying procedures, which effectively safeguard hydrophilic polymers and facilitate the formation of solid powders, hence leading to an increase in drug solubility.	2019	[15]
3	Vardenafil	Nanoparticles, transdermal administration (*in vitro* studies)	Approach dispersion with chitosan, polyethylene glycol and tetraethyl orthosilicate	The particle size is 440.5 nm, the zeta potential is 26.0 mV, the high vardenafil EE% is 71.5%, the suitable Q0.5% is 39.5%, and the high Q12% is 91.5%.	The chemical demonstrates favorable biocompatibility, a relatively acceptable safety profile, and is not expected to cause skin irritation when used topically. Pharmacokinetic characteristics indicate that bioavailability is higher when taken orally compared to oral delivery.	2022	[6]
4	Flibanserin	Nanocrystals, orally administration at a dose of 4 mg/kg BW of rabbits	Freeze drying with Technique soniprecipitation with surfactants PVP K30 and Pluronic F127	The particle size ranges from 312.53±4.60 nm to 640.45±13.40 nm. The zeta potential is-20 mV. The solubility ranges from 19.54±2.33 mg/L to 23.48±4.5 mg/L, which is approximately 5 times higher than that of pure flibanserin (4.32±0.56 mg/L). A decrease in peak sensitivity suggests a reduction in the number of crystals, specifically spherical crystals.	The dissolving speed and bioavailability have doubled, making it suitable for treating female hypoactive sexual desire disorder.	2021	[16]
5	Insulin growth factor 1	PLGA microspheres, injection administration	Water/oil/water(W1/O/W 2)emulsion technique	The loading efficiency is 63%, and by the end of day 14, 52% can be discharged.	Direct application of IGF-1 at the site can enhance erectile function following an injury.	2019	[17]
6	Eurycomanone	Nanoparticles, injection administration at a dose of 0,2 ml/100 g containing of drug 0,137 µg/g of C. magur	Gelasi ionic with chitosan and sodium tripolyphosphate	The particle size is 130 nanometers, the zeta potential is+49.1 millivolts, the particles have a spherical form and are well disseminated, and the encapsulation efficiency is 72%. Chitosan and Eurycomanone are connected via a conjugate bond.	Enhanced fecundity in fish due to elevated levels of hormones, including Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and progesterone.	2019	[18]
		Nanoparticles, injection administration at a dose of 0,2 ml/100 g containing of drug 0,137 µg/g of C. magur	Gelasi ionic with chitosan and sodium tripolyphosphate	The particle size is 130 nanometers, the zeta potential is+49.1 millivolts, the particles have a spherical form and are well disseminated, and the encapsulation efficiency is 72%. Chitosan and Eurycomanone are connected via a conjugate bond.	Enhanced levels of reproductive hormones and fertility to facilitate faster and safer conception at the prescribed dosage.	2019	[19]
		Nanoparticles, injection administration at a dose of 0,2 ml/100 g containing of drug 0,137 µg/g of C. magur	Gelasi ionic with chitosan and sodium tripolyphosphate	The particle size is 130 nanometers, the zeta potential is+49.1 millivolts, the particles have a spherical form and are well disseminated, and the encapsulation efficiency is 72%. Chitosan and Eurycomanone are connected via a conjugate bond.	No toxicity to the testis at a concentration of 0.137 µg/g	2018	[20]
7	Curcumin	Nanoparticles, transdermal administration at a dose of 200 mg in rats	Doped silicate sol-gel was lyophilized and wet-milled to generate an aqueous dispersion	Particle size 125 nm	Curcumin nanoparticles demonstrate potential in mitigating erectile dysfunction in mice models of type 2 diabetes; The application of abdomen pads topically can serve as a preventive measure against erectile dysfunction.	2018	[8]
8	Icariin	Nanospheres, orally administration at a dose of 50 mg/kg BW of rats	Zein Nanopartikel and TPGS	The particle size is 224.45 nm, with a polydispersity index of 0.34. The zeta potential is 0.961 mV, and the drug entrapment is 65.29%. The particles are spherical and amorphous crystalline in nature.	The medication can be delivered at the beginning and then slowly, during 24 h of release 82.3± 6.1% (*in vitro* test); At a safe dose (non-toxic) and increased sexual behavior in male rats at a dose of 20 mg/kg	2022	[7]

Manufacturers use polymeric nanoparticles to manufacture icariin nanospheres. Manufacturers utilize D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) in manufacturing because it enhances spleen transport and is suitable for formulating medications, particularly those classified as BCS class II and IV. In the production of icariin nanoparticles, researchers utilize sodium deoxycholate (SDC) and zein nanoparticles. When more TPGS, zein, and SDC are added, the nanospheres become smaller. This happens because these polymers are used. An elevation in the concentration of zein and a reduction in TPGS and SDC result in an augmentation of the zeta potential value. The entrapment efficiency (EE) is directly proportional to the amount of zein but inversely proportional to the amounts of TPGS and SDC [7].

Chitosan, a polymer with biocompatible and biodegradable characteristics, is employed to achieve the synthesis of eurycomanone nanoparticles, as well as to facilitate controlled release [20]. Chitosan-coated nanoparticles have been shown to enhance drug delivery compared to uncoated nanoparticles [30-32]. Chitosan exhibits minimal toxicity and its primary amine group can be chemically altered with appropriate ligands to enable precise and targeted release [33, 34]. Chitosan can enhance the absorption of drugs in the intestines by interacting with mucin glycoproteins in mucus. This interaction occurs through electrostatic interactions, as the positively charged chitosan strongly interacts with the negatively charged mucin glycoproteins. As a result, the interaction between positively charged chitosan and negatively charged mucin glycoproteins prolongs the residence time of materials in the intestines, increasing drug concentration at the absorption site [35]. Tripolyphosphate (TPP) serves as a crosslinking agent and hydrogen binder. A higher concentration of TPP leads to a lower particle size due to the increased density of ionic crosslinking, resulting in more compact and stable nanoparticles [20].

The selection of the preparation procedure will dictate the dimensions of the resultant particles. In addition, the properties of the produced nanoparticles are significantly influenced by the choice of polymers. Chitosan is a frequently utilized polymer capable of generating nanoparticles that possess desired features in accordance with specified criteria.

Topical dan oral administration of aphrodisiacs nanoparticles

Avanafil nanosponges, when taken orally, have shown a 2.5-fold enhancement in bioavailability compared to existing products. Consequently, avanafil nanosponges can be employed to decrease the required dosage. The utilization of cyclodextrin β-CD can enhance the oral bioavailability and efficacy of avanafil [4]. The administration of tadalafil solid dispersion can enhance the maximum plasma concentration (Cmax) and decrease the time to reach the maximum concentration (Tmax) due to an increase in solubility and a faster dissolution rate. A high area under the curve (AUC) value suggests rapid drug absorption following drug release. An extended duration of high drug concentration in plasma suggests an elevation in the bioavailability of tadalafil [15].

Researchers have found that tadalafil nanocrystals improve the sexual behavior of test animals and have a much higher maximum concentration (Cmax) than other products on the market. Similarly, the AUC_{0-48} is notably greater in comparison to existing drugs, showing an enhanced oral bioavailability of tadalafil [14]. Pharmacokinetic tests of flibanserin showed a twofold increase, indicating that the drug's oral bioavailability was enhanced due to a fivefold increase in its solubility. Expedited initiation of pharmacological effects and circumvention of inconsistencies in the oral intake of pharmaceuticals can be achieved [16]. Sildenafil nanoparticles have the potential to serve as an effective vehicle for the extended release of sildenafil citrate, leading to improved absorption when taken orally [36].

Dipropylene glycol is the most effective solvent for transdermal tadalafil formulations in terms of permeability, surpassing other solvents. When dipropylene glycol is used in transdermal tadalafil, it shows that the parameters of solubility and permeability are different *in vitro*. Tadalafil exhibits the lowest solubility relative to other solvents, although it demonstrates the maximum permeability. This can have the benefit of minimizing skin irritation. Utilizing cationic enhancers in transdermal administration can boost the permeability of tadalafil, but anionic enhancers reduce its permeability [1].

Permeation experiments of vardenafil with silica nanoparticles revealed a substantial enhancement in the speed of vardenafil permeation as compared to pure vardenafil. The histopathological study revealed no alterations in the epidermis and dermis layers of the skin. Topical administration of this substance does not result in obvious skin irritation symptoms, indicating its safety and good biocompatibility for use on the skin. Transdermal administration in the physiologically based pharmacokinetic modeling (PBPK) model results in a lower maximum concentration (Cmax) compared to oral administration. However, the time to reach maximum concentration (Tmax) and the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) are larger for transdermal administration than for oral administration. Transdermal delivery of silica nanoparticles can enhance the bioavailability of vardenafil and enable controlled and extended-release [6].

The small size of the vesicles enhances penetration by increasing the interaction with the corneocytes and the amount of medication that permeates the skin. This is due to the huge surface area resulting from the nanosize of the vesicles [37]. Pharmacokinetic tests conducted on rats demonstrated a roughly two-fold increase in the bioavailability of vardenafil when administered by transdermal films as compared to an oral drug suspension. Vardenafil ethosome (VRD-NE) transdermal films offer the advantage of lower dosages and diminished adverse effects, making them a potential treatment option for erectile dysfunction (ED). VRD-NE transdermal films are a highly promising transdermal drug delivery technology for the treatment of ED) that has the potential to enhance patient tolerance and adherence [38]. The optimized sildenafil nano-transpersonal films demonstrate greater permeability and diffusion coefficients compared to the control films. This indicates their ability to enhance and regulate the passage of sildenafil through the skin, potentially improving its transdermal delivery and bioavailability [39].

Curcumin nanoparticles, when applied topically, demonstrated the ability to penetrate the outermost layer of the skin, known as the stratum corneum, after 1 hour. Furthermore, the medication remained present in the hair follicle at a deep level even after 24 h. This prolonged presence of the drug enables its gradual release into the bloodstream over an extended period of time. Transdermal administration of curcumin can result in a 10^6-fold increase in curcumin levels in the plasma compared to intravenous injection. Curcumin's limited solubility restricts the amount that can be given. The effectiveness of curcumin nanoparticles was demonstrated by the enhancement of erectile function in experimental animals administered curcumin nanoparticles as compared to those given empty nanoparticles [8]. Curcumin nanoparticles have the ability to significantly enhance the water solubility and bioavailability of curcumin and copper complexes [40].

Nanoparticles can serve as transdermal aphrodisiacs due to their enhanced permeability and prolonged systemic circulation. The characteristics of solubility and permeability *in vitro* are distinct; hence, the choice of solvents and enhancers is a crucial issue to be taken into account while formulating transdermal formulations. When administering a drug orally, it is crucial to consider its solubility, as it directly affects the pace at which the drug dissolves.

Application of nanoparticles in herbal medicine as aphrodisiacs

Some of the most interesting things about natural products are their wide range of chemicals and biological functions, such as their ability to interact with macromolecules and be less toxic. Distributing drugs, even ones with big parts, can be hard because they aren't absorbed fully by the body, they're unstable *in vivo*, they don't dissolve well, they don't reach the right place in the body, they don't work as well as they could, and they might even have bad effects. Conversely, numerous natural substances fail to go through the clinical testing phases [41].

Eurycomanone nanoparticles can turn on the expression of genes involved in the steroid hormone pathway in test animals. This is

done by enzymes, which causes the production of androgens and estrogens in a cycle. Compared to the group that did not undergo any experimental treatment [18], the microscopic examination of the ovaries showed a faster development of oocytes. The concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) exhibited a considerable increase as compared to the control group and remained at consistent levels. The reproductive variables, such as fertilization rate, hatching rate, and survival, exhibited greater values compared to the control group when administered with an ovatide injection. Furthermore, using eurycomanone nanoparticles greatly improved the movement, concentration, and shape of sperm in mice. When administered at lower doses, this medication can enhance reproductive outcomes, and it can also be used as a standalone treatment.

In the Research found that orally administering nanospheres containing icariin is safe and non-toxic. The nano-formulation reduces mount latency time and ejaculation latency by nearly 50%, and decreases intromission latency time by approximately 41% compared to unprocessed icariin. These findings demonstrate that by decreasing the size of the icariin nanospheres, adjusting the zeta potential, and maximizing the efficiency of entrapment during their production, the delivery and effectiveness of icariin can be enhanced [42].

Converting herbal substances into nanoparticles enhances their effectiveness and bioavailability as aphrodisiacs, while also reducing the required dosage. Utilizing natural resources, the ionic gelation method produces nanoparticles. Particle size reduction strategies can enhance the solubility of natural materials. If the medicine has low solubility, transdermal administration of nanoherbs would be more advantageous compared to oral administration.

CONCLUSION

Researchers extensively utilize particle size reduction techniques for aphrodisiacs, encompassing both synthetic and natural components. Various techniques have demonstrated the ability to enhance the drug's bioavailability by generating nanoparticles. Patients can ingest or apply aphrodisiac nanoparticles topically to achieve regulated medication delivery. Nanotechnology will advance in the future to create medications that exhibit heightened efficacy, reduced toxicity, and prolonged release for targeted tissues.

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AUTHORS CONTRIBUTIONS

Dwi Saryanti: The process of conceptualizing or forming abstract ideas or concepts, Writing-Initial draft and Revision. Muhammad Da'i: Academic editor, Review, and Supervision, Erindyah Retno W: Corresponding author, Writing-Review and Editing and Supervision.

CONFLICT OF INTERESTS

There are no conflicts of interest among all the contributors

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