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FROM OCEAN TO OVARY: MARINE BIOACTIVE-BASED MUCOADHESIVE IN-SITU GEL AS A NOVEL THERAPEUTIC STRATEGY FOR PCOS

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ABSTRACT

Polycystic ovary syndrome (PCOS), is among the most common hormonal and metabolic disorders in women of childbearing age. This condition is marked by hormonal imbalance, resistance to insulin, ongoing inflammation, and oxidative stress. Traditional medical treatments, such as insulin sensitizers and hormone therapies, mainly aim to alleviate symptoms and can lead to various systemic side effects, limited effectiveness, and low patient adherence. As a result, there is a growing interest in alternative treatment methods that address multiple underlying issues at once. Oceanic habitats hold a wealth of unique bioactive substances, including polysaccharides, carotenoids, peptides, and polyphenols, many of which offer antioxidant, anti-inflammatory, and metabolic benefits that can aid in managing PCOS. Nevertheless, the use of these substances in clinical settings is often restricted due to their poor stability and bioavailability. Mucoadhesive in-situ gel systems have been recognized as effective drug delivery methods that can ensure localized, sustained, and controlled release of medication, while also improving mucosal attachment and reducing overall systemic impact. This narrative review examines the underlying mechanisms and treatment targets of PCOS, evaluates the therapeutic potential of marine-derived bioactive substances, and considers the advantages of mucoadhesive in-situ gel formulations for enhancing drug delivery. Combining marine pharmacology with innovative biomaterial-based

delivery techniques may provide a new, focused, and patient-friendly approach for effectively managing PCOS.

KEYWORDS: Polycystic Ovary Syndrome (PCOS), Marine Bioactives, Mucoadhesive In-Situ Gel, Marine-Derived Polymers, Chitosan, Alginate, Carrageenan, Intravaginal Drug Delivery, Controlled Drug Release, Oxidative Stress, Insulin Resistance, Anti-inflammatory Therapy.

INTRODUCTION

Globally, one of the most common endocrine-metabolic diseases in women of childbearing age is Polycystic Ovary Syndrome (PCOS), which is also referred to as Polycystic Ovary Disease (PCOD).[1] A group of hormonal, metabolic and reproductive abnormalities, such as irregular menstrual cycles, hyperandrogenism and polycystic ovarian morphology, are features of the complex disorder. The prevalence of PCOS has been reported to range between 4%-21% in women across different countries globally. These variations are primarily due to different diagnostic criteria used and different populations studied. Besides being so common, PCOS is a major public health concern because it leads to infertility and has been associated with increased risk for metabolic problems such as obesity, cardiovascular disease, type 2 diabetes mellitus and cancer of the endometrium.[1,2]

The pathogenesis of PCOS is complex and occurs due to the combined effect of several factors. These include **genetic predisposition, environmental influences, and lifestyle-related disorders**, all of which interact with each other and contribute to the development of the condition. It is underpinned by the hypersecretion of LH, which causes theca cells in the ovaries to produce testosterone [in excess] and results in ovulatory dysfunction. In simple terms, there is an inherited tendency for some patients with PCOS, and this condition will also be triggered if their family are subjected to stressful conditions, leading to the ovaries getting tired quickly and fail to produce eggs when required. However, recent studies have shown that the actual cause probably affects receptors located over several organs, such as the brain, especially at sites where hunger signals, i.e., insulin hormone receptor found.

The ultimate goal of the current pharmacological management of PCOS is symptom control. Despite being indicated for the treatment of insulin resistance and the restoration of ovulation, insulin sensitizers including metformin cause significant gastrointestinal side effects, have poor patient adherence, and are often ineffective.[12] Hormonal agents such as

OCPs are useful for regularizing menstrual periods and reducing androgenic symptoms. However, they cannot be used in women who wish to conceive and carry the risk of thromboembolism.[6] Ovulation induction agents like clomiphene citrate are also widely used but face problems of resistance and poor efficacy. More importantly, the current therapeutic modalities are not very effective because they do not target these newer pathological mechanisms that have recently emerged to play a central role in the pathogenesis of PCOS — oxidative stress and chronic inflammation. Moreover, systemic drug administration frequently leads to side-effects and non-compliance issues.[7]

Given these constraints, the increasingly urgent issue of developing new therapeutic drugs to more effectively manage the myriad facets of PCOS along with decreasing side effects associated with their use, has therefore resulted in a focus on the potential utility of natural compounds with anti-inflammatory, antioxidant and metabolic regulating properties. Unfortunately, the practical translation of many such drugs is limited due to their lack of targeted delivery systems, fast degradation and low bioavailability.[8]

A promising solution is offered by advanced drug delivery systems such as mucoadhesive in-situ gels, where drugs can be released in a sustained and localized manner with improved mucosal retention and minimal systemic absorption. These gels can undergo a sol-gel transition in response to physiological cues providing controlled release as well as prolonged drug residence time which can be advantageous especially in the field of gynaecology.[9]

Most noteworthy, bioactive compounds obtained from the marine source are structurally diverse with significant bioactivity profiles. Marine derived compounds namely polysaccharides, peptides, alkaloids, polyphenols etc., possess robust antioxidant, anti-inflammatory, immunomodulatory and endocrine modulating activities which are suitable for PCOS therapy.[10] This review proposes that if such marine bio actives can be formulated into advanced delivery systems like mucoadhesive in-situ gels; challenges pertaining to their stability and bioavailability could be eliminated. As a result therapeutically effective formulations can be developed. Thus treatment modalities for PCOS which are safe, effective and patient compliant may become feasible due to this multidisciplinary approach of merging marine pharmacology with biomaterial science.[11]

This review attempts to fill this very important gap and puts forth an overview of drawbacks associated with available pharmacological treatment modalities. A detailed discussion on the

global prevalence and etiopathogenesis of polycystic ovary syndrome, coupled with a focus on the potential utility of marine-based bio actives as prospective pharmaceutical aid is provided. Furthermore, a review on unconventional application of mucoadhesive in-situ gel formulations for facilitating enhanced drug delivery will be discussed to outline possible future therapeutic strategies aimed at overcoming identified gaps in the existing management approach for PCOS.

Pathophysiology and Therapeutic Targets in PCOD/PCOS

Ovarian Dysfunction and Hormonal Imbalance

The hypothalamic-pituitary-ovarian (HPO) axis is disrupted in Polycystic Ovary Syndrome (PCOS), also known as Polycystic Ovary Disease (PCOD). Normally, the anterior pituitary secretes follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in response to pulses of gonadotropin-releasing hormone (GnRH). Luteinizing hormone stimulates a mid-cycle surge that mediates ovulation, while FSH supports follicular growth and maturation.[12] GnRH's pulsatility is altered in PCOS, causing greater secretion of LH than FSH. The excessive levels of LH overstimulate the ovarian theca cells, increasing production of androgens such as testosterone and androstenedione. The increased androgens inhibit granulosa cell function as well as downregulate aromatase activity, an enzyme that converts androgens into estrogens. Thus, hyperandrogenism impairs follicular maturation which ultimately causes anovulation. This hormonal disturbance results in anovulatory cycles, polycystic ovarian morphology (PCOM), and follicular arrest.[12]

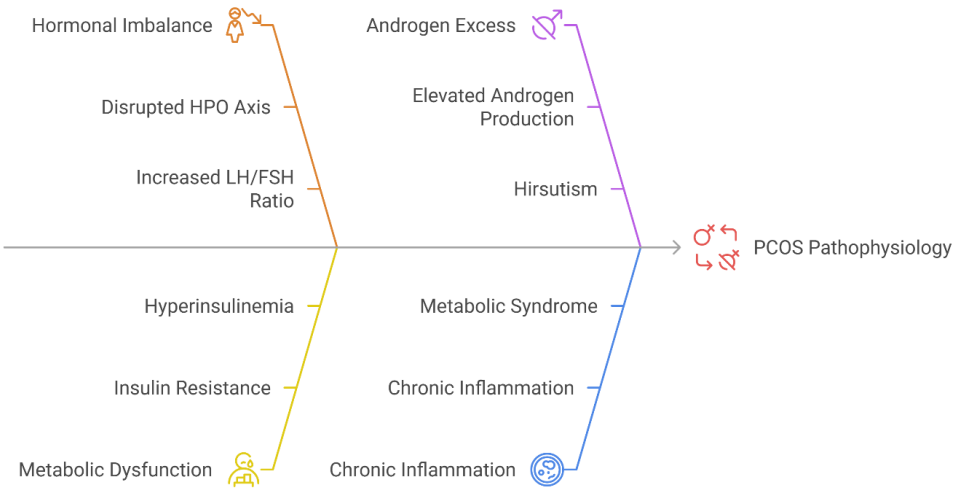

Fig 1: Pathophysiological Mechanisms Underlying Polycystic Ovary Syndrome (PCOS).

Role of Insulin Resistance and Metabolic Dysfunction

Irrespective of whether they are obese or not, approximately 70% of women with PCOS are insulin resistant (IR), which is the principle metabolic imbalance of the disorder. The insulation resistance in the peripheral tissues, in muscle, adipose tissue and liver, impairs the insulin signalling, leading to hyperinsulinaemia observed in PCOS.[14] The hyperinsulinaemia is a consequence of the hypersecretion of insulin by the pancreas to overcome insulin resistance. This implies that the LH and the insulin work together, the LH stimulates production of male hormones, and the increased insulin bioavailability suppresses SHBG that carries testosterone.[15]

Additionally, disordered adipose tissue with the resultant increased free fatty acid and adipokine release can further exacerbate metabolic dysfunction in PCOS, thereby increasing the risk of development of both metabolic syndrome/type 2 diabetes and cardiovascular disease as well as systemic low-grade inflammation.[14,15]

Oxidative Stress and Chronic Inflammation

Chronic low-grade inflammation and oxidative stress are increasingly recognized as important contributors to the pathophysiology of PCOS. Independent of adiposity, women with PCOS present higher pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and reactive oxygen species (ROS).[16]

Insulin resistance and metabolic dysfunction are further aggravated by these inflammatory mediators that also impede insulin receptor signalling pathway. Moreover, oxidative stress damages ovarian microenvironment weakening follicular cells and oocytes which affects reproductive outcomes as well as persists hormonal imbalances.[16,17]

Potential Therapeutic Targets

Given PCOS's intricate, multifaceted pathogenesis, several treatment targets are essential:

• ***Hormonal Modulation***: To restore regular ovulation, treatment focuses on lowering elevated testosterone and re-establishing normal LH/FSH relation. For this purpose oral contraceptives and anti-androgens are used.[18]

• ***Insulin Sensitization:*** Drugs like metformin decrease ovarian androgen production, reduce hyperinsulinemia, and increase peripheral insulin sensitivity.[14]

• ***Anti-Inflammatory and Antioxidant Actions:*** Insulin signalling and ovarian functions can be modified by overcoming oxidative stress and chronic inflammation. For this purpose, bioactive chemicals and natural antioxidants are under exploration.[16]

• ***Ovarian Follicle Regulation:*** Granulosa and theca cell function must be altered to promote selection of the dominant follicle and prevent follicular arrest to re-establish regular ovulatory menstrual cycles.[19]

Relevance of These Targets for Drug Development

The complicated etiology of PCOS requires multi-targeted treatment approaches that ought to be capable of meeting the needs of oxidative stress, inflammation, metabolism dysfunction, and hormonal disorders. Nevertheless, the complex etiology of the syndrome in the majority of the cases might not be completely undone under the existing pharmaceutical therapy which tends to focus on certain aspects of the syndrome.[20] This has led to the interest in designing novel molecules, such as bioactives of sea origin with simultaneous anti-inflammatory, anti-oxidative and metabolic controlling effects.

Furthermore, new drug delivery systems such as mucoadhesive in situ gels can provide promising possibilities to improve stability, bioavailability and target delivery of therapeutic agents. Toward the precision medicine and individualized treatment strategies for PCOS patients, these may increase drug efficacy while reducing systemic side effects and enhancing patient compliance.[20,21]

Marine Sources: A Reservoir of Bioactive Compounds

Overview of Marine Biodiversity and Pharmacological Potential

One of the richest and most diverse ecosystems on our planet- the ocean, encompasses 70% area of the Earth. Marine biodiversity nature still remains a mystery too as this ecosystem is not yet completely studied or explored. Ranging from bacteria, algae to fish and invertebrates, survival in extreme environments have made certain species very unique which include high pressure, varying salinity, low temperature and nutrient availability where they call home. Hereby new chemical entities with unique structural features as well as biological functions that are not found among terrestrial organisms have evolved over time. An example of such products would be Ziconotide compared from land-based organisms.[21]

These unique marine natural products (MNPs) are promising leads for pharmaceutical development due to their diverse bioactivities. In the last few decades, a number of drugs

based on chemicals derived from marine sources have been successfully developed and marketed particularly for the treatment of cardiovascular diseases, infectious diseases and cancers. The anticancer drug ziconotide (from the venom of cone snails) and trabectedin (from sea squirts) serve as two such examples. These successes clearly underscore that an immense chemical diversity lies untapped in the oceans which can be harnessed to combat complicated disorders such as PCOD/PCOS.[21,22]

Marine-Derived Compounds

Many bioactive molecules possessing properties, which are most relevant for the cure of PCOS are being synthesized by the different marine species. Some of them include

• ***Polysaccharides:*** Polymers with remarkable mucoadhesive and biocompatible properties, such as alginate (from seaweed), carrageenan and chitosan (from crab shells), which are good candidates for drug delivery systems, for example in-situ gels that can adhere to mucosal surfaces, enable controlled release of drugs. In addition, various marine polysaccharides possess anti-inflammatory and antioxidant activities that help combat inflammation and oxidative stress related to PCOS pathophysiology.[23]

• ***Marine Polyphenols and Carotenoids:*** Known for their potent anti-inflammatory and antioxidant properties, marine algae produce carotenoids (e.g., astaxanthin) and polyphenolic compounds (e.g., eckol). These compounds can exert an anti-oxidative stress effect, ROS scavenging, and pro-inflammatory cytokines downregulation to alleviate two risk factors of PCOS pathological process development.[11]

• ***Peptides and Alkaloids:*** A number of peptides and alkaloids extracted from marine sources were found to alter metabolic control and hormone pathways, useful in treating hormonal imbalances and metabolic dysfunction common in PCOS due to their interactions with endocrine receptors and signaling molecules.[11]

• ***Fatty Acids:*** Insulin-sensitizing, anti-inflammatory and ovarian-protective effects of omega-3 polyunsaturated fatty acids (PUFAs), derived from marine algae and fish oils (DHA and EPA) have been well explored. Omega 3 supplements are important therapeutic agents with clinical evidence showing the reduction in the levels of androgens, improvement in insulin resistance as well as reduction in systemic inflammation among women with PCOS.[8]

Potential of Marine-Derived Agents for PCOD/PCOS Management

Several marine isolates are found to be antioxidants, which decrease oxidative stress of ovarian tissues, thereby assisting in the amelioration of hormonal balance and follicular condition.[25] The chronic low-grade inflammation linked to insulin resistance and metabolic defects in PCOS is inhibited by anti-inflammatory activity of metformin.[11] Most substances contain characteristics that increase the body sensitivity to insulin and hence improve and improve glucose breakdown and reduce hyperinsulinaemia, which is considered the primary determinant in the pathophysiologic of PCOS.[20]

Some few marine bioactives are also anti-androgenic that could be useful in restoring ovulatory activity and lowering elevated levels of testosterone.[20] The marine products compound is a way out of the traps of the traditional synthetic drugs. They have several targets which they can easily rectify the intricacy and interrelationship of disturbances present in PCOS and high biocompatibility resulting in insignificant side effects.[20,25]

Examples of promising marine bioactives

• ***Fucoidan:*** Extracted from brown seaweed, it is a sulphated polysaccharide that shows beneficial metabolic parameters related to PCOS and possesses strong inflammation and oxidation combating properties.

• ***Chitosan Oligosaccharides:*** Though not well known, these oligosaccharides are derived from chitosan and suit the treatment of PCOS because they improve insulin sensitivity and reduce inflammation.

• ***Astaxanthin:*** A potent marine carotenoid which enhances oocyte quality and hormonal profiles in PCOS through reduction of oxidative stress and endoplasmic reticulum stress in ovarian granulosa cells.

• ***Eckol:*** It is a polyphenol derived from brown algae. It has both anti-inflammatory and antioxidant effects which suggests it should be able to support ovarian health and function.

When together these are substances of marine origin they present a possible substitute to the existing treatment of PCOS or can also act as supplement in this regard which is specifically true when these substances are integrated with highly advanced delivery systems such as mucoadhesive in-situ gels for increased targeting and sustained release.[25]

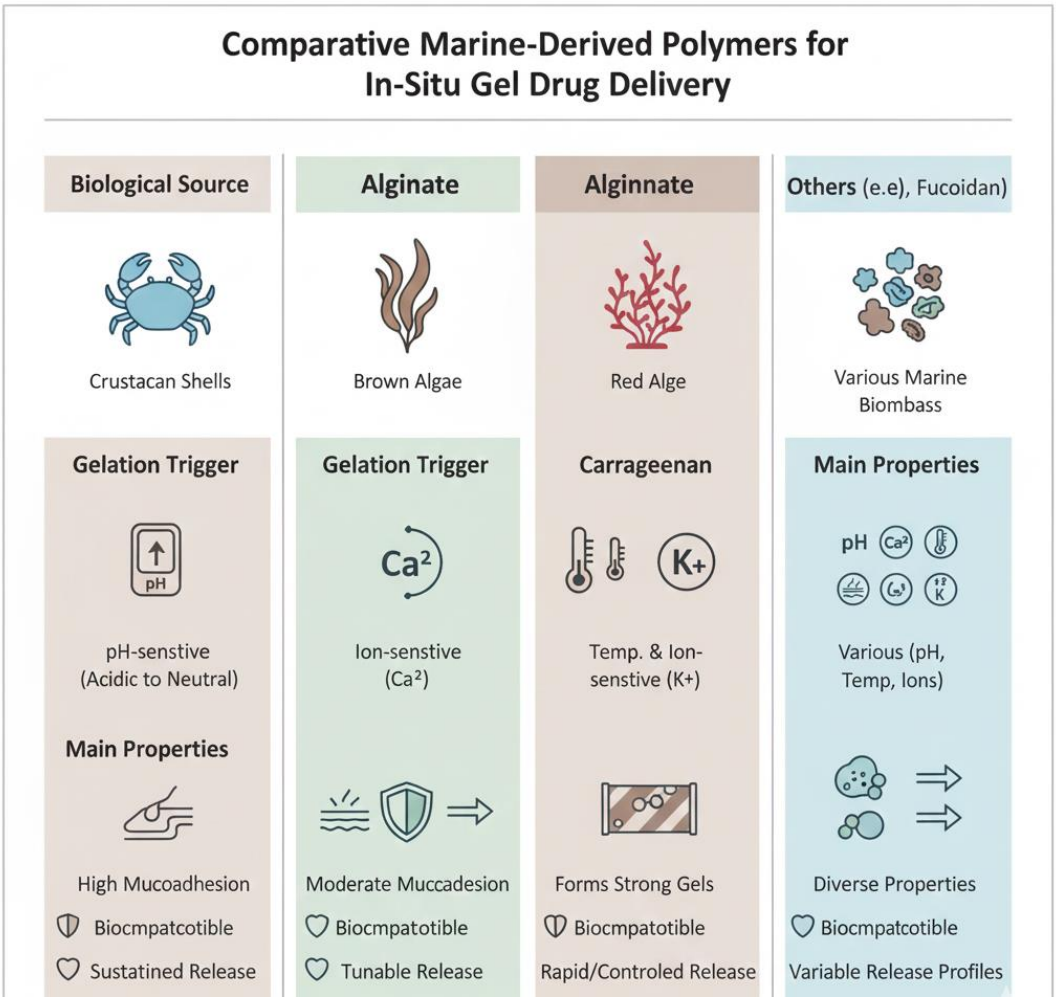

Fig. 2: Comparative Overview of Marine-Derived Polymers Utilized in In-Situ Gel Drug Delivery Systems.

Mucoadhesive In-Situ Gel Systems: A Detailed Overview

Concept and Mechanism of In-Situ Gelling Systems

In–situ gelling systems are liquid formulations which are relatively new and upon application to a specific physiological location undergo a sol–gel phase transition. This transition is triggered by the physiological parameters such as temperature, pH or ionic content of the body and hence these are commonly known as sol–to-gel transitions. The transition takes place in-situ i.e., at the site of action, producing a semi-solid gel which remains at the administration site for prolonged duration. This feature considerably enhances the residence time of the formulation ensuring controlled and sustained release of encapsulated drug. In case of mucosal routes like vaginal, nasal, ocular, buccal and rectal administration where retention and targeting effect are crucial for therapeutic effect, in-situ gels are particularly advantageous.[26]

Depending on the polymer and the environmental trigger, the gelation mechanism is different. Temperature responsive systems remain liquid at ambient temperature while form gels at body temperature. These include poloxamers (Pluronic® F127 and F68) which form micellar networks upon heating at physiological temperatures. Due to dehydration of polymer chains several cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose (HPMC) exhibit reversible gelatinationpon increase in temperature.[27] Moreover, the pH-sensitive systems depend on the pH of the surrounding environment to gelation. One of the most popular examples is Carbopol which is a cross-linked polyacrylic acid polymer. When exposed to the physiological solid gel. At an acidic pH, the polymer chains temperature are coiled, and the solution hypersensitive behaviour reminds that of phenol red; thus stays fluid. Therefore, Because of this mechanism pH-responsible devices are perfect for drug delivery via vagina, nose or eye where gelation may be triggered by pH difference between formulation and physiological fluids.[28]

When exposed to physiologic ions such as Ca2+, Na+, or K+, they gel. When exposed to these ions, polymer systems such as Gellan gum and sodium alginate undergo ionic crosslinking, a situation that leads to the formation of relatively firm but flexible gels. This is explained by the “egg-box” model for the interaction of calcium with alginate, in which blocks of guluronic acid residues associate with calcium ions along the polymer chain to form a gel matrix. By producing gels in situ, systems based on these polymers can be injected through a narrow bore needle, so their use in vaginal and ocular formulations is particularly suited. A fourth type of system that relies on swapping aqueous physiologic fluids for the formulation solvent to precipitate or gel a network also is possible cases natural ion concentrations are enough to initiate the coagulation process.[25]

The most important advantage of in-situ gel systems is the presence of a dual-phase feature. Gels combine the retention and sustained release properties, while liquids are easy to administer. The continuous release provides constant therapeutically effective levels and a prolonged cutaneous presence on mucosae reducing elimination and enhancing absorption process of drugs as well. Moreover, these strategies will enhance patient compliance and convenience by increasing local bioavailability as well as minimizing dosing frequency.[26]

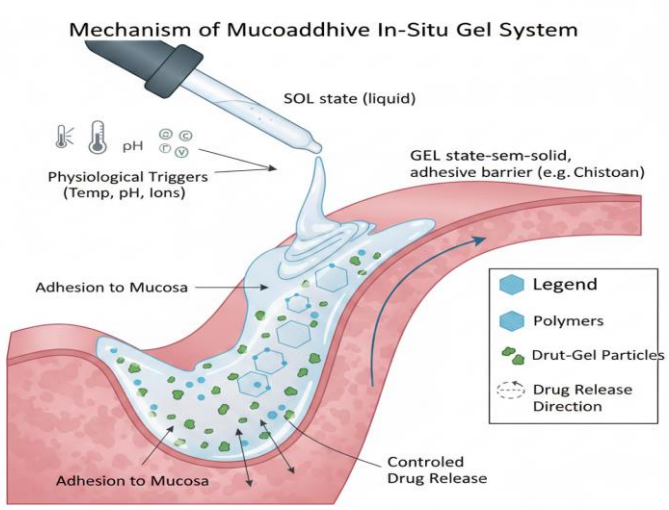

Fig. 3: Schematic Representation of Marine-Derived Mucoadhesive In-Situ Gel Formation and Drug Release at the Mucosal Site.

Mucoadhesive Polymers

The capacity of a polymeric material to adhere to mucosal tissues through non-covalent interactions such as hydrogen bonds, electrostatic attraction and van der Waals force is called mucoadhesion. These interactions are facilitated by the presence of mucus layer which is primarily composed of mucin glycoproteins. The formulation therefore remains attached for extended periods of time. Mucoadhesive polymers enhance uptake of drug both locally and systemically, reduce clearance by physiological fluids and enhance retention of in-situ gelling systems.[29]

Owing to their biocompatibility and biodegradability, natural mucoadhesive polymers such as chitosan, sodium alginate, gellan gum and pectin have gained considerable attention. Chitosan, a cationic polymer obtained by deacetylation of chitin, can electrostatically interact with negatively charged mucin and shows excellent mucoadhesive properties.[28]

Moreover, it may temporarily open tight junctions i.e. augment drug delivery and mucosal permeation in a drug carrier12. Sodium alginate of brown algae is divalent cations forming strong gels and adheres by hydrogen bonding hence applicable in vaginal and nasal preparations29. The microbial polysaccharide gellan gum which comprises of ionically cross-linked gels possesses strong mucoadhesion and good mechanical properties. Plant derived polymer pectin is also common in the delivery of oral and vaginal drugs since it is a natural polymer that forms calcium-mediated gels due to its natural origin and safety28[U].

Synthetic polymers like Carbopol, Polycarbophil, hydroxypropyl methylcellulose (HPMC) and Polyvinyl alcohol (PVA) offers more control over viscosity, swelling behaviour, and adhesion strength. Both polyacrylic acid derivatives; Carbopol and polycarbophil form extensive hydrogen bonding with mucin rendering them high mucoadhesive strength.[30] Polyvinyl alcohol (PVA) and polyethylene glycol (PEG) is used as viscosity enhancers and stabilizers in combination systems while HPMC; a non-ionic cellulose ether increases gel stability and viscosity along with guar gum. The desired rate of drug release, site of administration and pH of the body fluid at the site determines the choice of polymer or polymer blend.[31]

There are many advantages of Mucoadhesive in-situ gels from pharmacokinetic point of view as it decreases elimination of the drug because of long term interaction with mucosa and thus enhances absorption. The controlled release profile ensures lower systemic side effects, reduced fluctuations in plasma concentration and increased efficacy due to maintenance of therapeutic concentration for prolonged duration. Localised effect delivered by using mucosal route helps to prevent metabolism by the first pass and hence reduces systematic toxicity.[32]

Routes of Administration Relevant to PCOD/PCOS

Mucoadhesive in-situ gel solutions provide versatile and patient-friendly approach for the management of Polycystic Ovarian Disease (PCOD) and polycystic ovarian syndrome (PCOS). Vaginal route is significant as it circumvents hepatic first-pass metabolism, possesses high vascularization, and offers targeted delivery to reproductive organs. These are site-specific delivery systems that help in administering hormones, insulin sensitizers, and antioxidants at specific sites to achieve control over endometrial and ovarian functions.[33] These formulations provide steady therapeutic levels of drugs, increased bioavailability locally, reduce systemic drug exposure, stay at the mucosal site due to adhesiveness, and release the drug gradually. For enhancing hormonal profiles and reproductive outcomes in PCOS conditions; drugs such as metformin, clomiphene citrate progesterone, myo-inositol have been studied after incorporation via this pathway.[34]

Other non-invasive strategies for systemic drug delivery are nasal and buccal routes. Both routes provide rapid absorption and systemic circulation since they do not undergo first-pass metabolism by the liver due to rich circulatory network and thin epithelial barrier. For hormonal or metabolic regulators such as insulin sensitizers and gonadotropins which required specific levels systemically for therapeutic effects, mucoadhesive in-situ gels

administered via nasal and buccal route are particularly useful. The mucoadhesive property provides prolonged contact time therefore enhanced drug bioavailability via avoiding fast clearance.[35,36]

Furthermore, oral mucoadhesive in-situ gels have been formulated for gastro-retentive delivery, presenting labile molecules with protection in the GI tract and sustained release. By this approach agents aimed at systemic metabolic abnormalities in PCOS such as insulin resistance and hyperandogenism can be applied. Metabolic control is further enhanced by regulated release from the gel matrix ensuring gradual absorption and long-lasting systemic activity.[37]

Marine-Derived Compounds as Mucoadhesive In-Situ Gel Components

Marine Polymers in In-Situ Gel Formulation

Unique biopolymers having a range of structural and functional features suitable for pharmaceutical applications are plentiful in marine environment. Marine polysaccharides comprise chitosan, alginate and carrageenan which have been explored significantly for designing mucoadhesive in-situ gel systems. These polymers, other than serving as gelling agents, also impart biocompatibility, biodegradability and enhanced mucoadhesion which are prerequisites for site-specific and sustained drug delivery via mucosal routes.[38,39]

A commonly known marine polysaccharides that has been studied for the formulation of in-situ gelling systems is chitosan. Chitosan is produced by partial deacetylation of naturally occurring chitin which is a structural component in exoskeletons of crustaceans such as shrimp and crabs. Linear cationic polymer consists of repeating units of N-acetyl-D-glucosamine and β-(1→4)-linked D-glucosamine, known as chitosan. The majority of natural polymers are neutral or anionic, however, this is not a case for chitosan which makes it unique among other natural polymers. Amino groups on chitosan are protonated in acidic medium allowing strong electrostatic interaction between mucin molecules (which are negatively charged) found at mucosal surfaces hence giving rise to macoadhesion where the composition showed greater mucoadhesive properties therefore prolong the residence time at application site.[40]

Also, chitosan gels are pH responsive. At neutral to slightly alkaline pH (e.g., in the intestine or vaginal mucosa), chitosan deprotonates and forms a gel. At acidic pH it is still soluble and liquid. Because of this pH-triggered sol-to-gel transition, chitosan-based systems are

particularly well-suited for in-situ gelling applications. In addition to its gel-forming capabilities, chitosan also has an inherent ability to transiently open tight junctions between epithelial cells thus enhancing penetration and facilitating drug transport across biological membranes. Chitosan gels alone, however, may not be mechanically strong; therefore incorporation with other polymers such as gellan gum or sodium alginate can improve their strength, stability, and drug release profile.[40,41]

Alginate, another widely studied polymer obtained from the sea, is extracted from brown seaweeds including Macrocystis, Ascophyllum and Laminaria. Alginate consists of binary blocks, either homopolymeric (M–M, G–G) or heteropolymeric (M–G), linear copolymers of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. Alginate displays a unique property since it can undergo ionotropic gelation in the presence of divalent cations such as calcium (Ca2+). The three-dimensional “egg-box” structure responsible for gelling is formed by coordination between carboxyl groups of guluronic acid blocks and calcium ions. Due to its rapid gelation process and physiological benignity, alginate is a promising polymer for preparation of in-situ gels for mucosal drug delivery.[42] Rewritten Text: Also raised from the sea, another polymer often discussed is alginate which is gathered from brown seaweeds such Macrocystis, Ascophyllum and Laminaria. Its blocks are binary consisting either homopolymeric (M–M, G–G) or heteropolymeric (M–G), linear copolymers of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. There’s something peculiar about alginate given it’s ability to ionotropically turn into a gel when exposed to divalent cations like calcium (Ca2+). The “egg-box” structures that does this gelling get formed as calcium ions attach themselves to the carboxyl groups located on guluronic acid block. Fast gelling process along with benign nature at physiological condition makes alginate an interesting polymer for making in-situ gel based on mucosal drug delivery.[42]

Alginate based gels can encapsulate drugs with both hydrophilic and hydrophobic nature due to its own hydrophilicity and biocompatibility. Polyelectrolyte complexes put together from both sodium alginate (negatively charged carboxylic groups) and chitosan (positively charged amino group), mucoadhesive in nature besides having controllable release trends along with high mechanical strength. The polymer complex systems have shown increased mucoadhesion, controlled release, and mechanical properties than individual polymer systems this make them more efficient candidate for vaginal & nasal drug delivery where both mucosal adhesion and structural integrity are required for therapeutic success.[42,43]

Another important marine-derived polysaccharide obtained from the red seaweeds (Rhodophyceae) is carrageenan. It can adopt several structural forms, mainly κ-, ι-, and λ-carrageenan, based on the amount and position of sulfate groups. It is comprised of sulfated galactose and 3,6-anhydrogalactose units. The gelling capacity of carrageenan at high temperature has been well studied. Carrageenan firstly forms sol in aqueous solution as the double-helical junction zones are generated and cation such as potassium or calcium to be a stabilizer, then cools into gel systems. Owing to this characteristic, the systems based on carrageenan are particularly advantageous for temperature-responsive in-situ gel compositions.[44]

The sulphate groups present in carrageenan are responsible for mucoadhesion and provides it with unique physicochemical properties. Hydrogen bonding and electrostatic interaction with mucin allows strong adhesion to mucosal surfaces by these groups. In addition, carrageenan forms transparent, elastic, and smooth gels which can be really useful in encapsulating drugs for sustained release over a period of time.[45]

Chitosan is inherently cationic and more permeable than these polymers, but gelation is typically achieved by a pH shift. Carrageenan provides thermosensitive gelling and high gel strength conducive to temperature-mediated administration, whereas alginate ionotropically gels in the presence of physiological ions to form strong hydrophilic matrices. For a formulation scientist, by judiciously combining these marine based polymers it is feasible to tune mucoadhesive properties, mechanical properties, and gelling kinetics for a specific drug and delivery system applications. Such hybrids not only promise reduced dosing frequency but also enhanced bioavailability, stability, and patient compliance.[44,45]

Marine Bioactives Incorporated in In-Situ Gels

These marine polysaccharides, many bioactive molecules retrieved from the marine species that are proposed as drugs along with the insitu gel systems are peptides, carotenoids, sulfated polysaccharides, and secondary metabolites which have anti-inflammatory, antioxidant, and hormone-regulating activities relevance to metabolic as well as gynecological disorder like PCOD and PCOS.

Marine Bioactives in capsules: In-situ gel systems have been successfully employed to encapsulate marine-derived compounds such fucoidan, astaxanthin and marine peptides. These bio actives are protected upon encapsulation within a gel matrix from enzymatic

degradation in vivo, and environmental degradation (pH, temperature and light). For example, Fucoidan, a sulphated polysaccharide isolated from brown seaweeds like *Undaria pinnatifida* and Fucus vesiculosus possesses anti-inflammatory, anticoagulant and antioxidant activity that can be combined with alginate–chitosan based in-situ gelling system for sustained release at efficient therapeutic concentration at the target site.[46,47]

In the same way, Astaxanthin encapsulated mucoadhesive in situ-gel can be developed which is a marine carotenoid having a powerful antioxidant activity used for enhancing stability and bioavailability. Due to its oxidation sensitivity & lipophilicity, protective polymeric network of gel prevents its degradation thereby allowing sustained on mucosal administration. This is particularly advantageous in disease conditions like PCOS which are associated with oxidative stress because topical antioxidant therapy can modulate hormone balance as well as inflammation.[47,48]

Extracted from fish, molluscs, and algae, marine-derived peptides have also been investigated for their anti-inflammatory[86] hormonal[87] and metabolic[88] benefits. These peptides increased the stability of marine polymer-based gels, inhibited enzymatic hydrolysis, and facilitated systemic or localized absorption via mucosal pathways.[43]

Long-Term Release and Prolonged Residency: In-situ gels of marine polymers inherently provide controlled and prolonged release of encapsulated bioactives. Mucoadhesion ensures extended interaction with mucosal tissue which leads to enhanced drug permeation and overall drug availability, while the gel network controls drug release. Both sustained release as well as prolonged residency offer advantage of maintaining therapeutic concentration in body for longer duration thereby reducing dosing frequency leading to better patient compliance, particularly required for treatment of chronic endocrine disorders like that of PCOS needing long term constant therapeutic management rather than short exposure to therapy.[50]

Example Formulations in Gynaecological and Hormonal Disorders: Chitosan–alginate composite in-situ gels containing marine-derived bioactives such as fucoidan or antioxidant peptides have recently been investigated in experimental studies for reproductive organ specific delivery. Oxidative stress and inflammation are two of the key pathogenic features of PCOD/PCOS which are significantly modulated by these formulations in addition to improved mucoadhesiveness and drug retention. A fucoidan-loaded chitosan–alginate gel was

designed for intravaginal administration to enhance local redox balance and re-establish hormonal equilibrium post oxidative stress therapy; with direct delivery of antioxidants to both ovarian and uterine sites. Analogously, thermosensitive carrageenan gels with astaxanthin or marine peptide encapsulation could become non-invasive delivery platforms, suitable for sustained release applications due to temperature-triggered gelation.[47,50]

Experimental Models for Evaluating Anti-PCOD/PCOS Potential

Reliable preclinical models that reproduce the pathophysiological, hormonal and metabolic malfunctions of PCOD/PCOS are required for the development of effective treatment strategies. So, in-vitro as well as in-vivo models must be used when testing potential anti-PCOS drugs, particularly if they are formulated into mucoadhesive in-situ gels, to assess pharmacodynamic effects, drug release, formulation properties and therapeutic effects.[51]

In-Vitro Models

Ovarian Granulosa Cell Cultures

Among various biological functions, GCs are well recognized as key regulators of steroidogenesis and follicular growth.[49] A direct and effective way to investigate the molecular deregulation and hypersecretion of steroids associated with PCOS is the use of human GC lines for in vitro studies. Human immortalized granulosa-like tumor cell line KGN, HGrC1, COV434 express FSH-r, aromatase (CYP19A1), and LH-r; therefore, the processes related to steroidogenesis, follicular maturation, and apoptosis can be studied.[50,51]

Granulosa cells often display enhanced oxidative stress, decreased aromatase activity and altered androgen receptor expression under PCOS conditions. The models enable to investigate the influence of potential formulations or bioactive compounds on estrogen production, cellular antioxidant defence and gene expression (CYP11A1, CYP19A1, STAR). Thus, at molecular level insights are obtained on folliculogenesis promotion and hormonal abnormalities correction by in-situ gels.[50,51]

Insulin-Resistant Cell Models

One of the hallmarks of PCOS is insulin resistance, which results in hyperinsulinemia and metabolic disturbances. Models of insulin resistance in vitro, such as 3T3-L1 adipocytes, C2C12 myotubes and HepG2 hepatocytes are generated under insulin exposure continually high-glucose or free fatty acid (palmitate) conditions. These models can be used to study

GLUT-4 translocation, glucose uptake rate along with PI3K/Akt, AMPK signalling pathway.[52]

Anti-PCOS medications to show the improved insulin sensitivity, reduced oxidative stress and return to metabolic normalcy could be subjected for testing these systems. Whether or not mucoadhesive in-situ gels with marine bioactives as fucoidan / astaxanthin lead to increased glucose uptake and modulate insulin receptor signaling hence providing assessment of metabolic correction at early stages could also be tested.[53,54]

In-Vivo Experimental Models

A systemic view of PCOS pathogenesis is offered by in-vivo animal models, which represent both metabolic and ovarian problems. Letrozole-induced, DHEA-induced, and estradiol valerate-induced PCOS models are frequently employed and each one captures different facets of the condition.[55]

Letrozole-Induced PCOS Model (Androgenic Type)

One of the most well-known and clinically relevant rodent models is the letrozole-induced PCOS model. Letrozole induces anovulation, development of cystic follicles and hyperandrogenism. It is a non-steroidal aromatase inhibitor that blocks the conversion of androgens to estrogens. The administration of letrozole (1 mg/kg/day) by gavage to female rats or mice during 21 days induces similar features observed in women with PCOS: irregular estrous cycles, increased serum testosterone levels and an increased LH/FSH ratio.[50] Using this model, formulations targeting ovarian dysfunction, androgen excess or hormonal balance can be evaluated.[51]

DHEA-Induced Model (Metabolic and Hormonal Type)

The model of PCOS produced by dehydroepiandrosterone (DHEA) mirrors both metabolic and hormonal changes seen in the disease. Subcutaneous administration of DHEA(6mg/100g body weight for 20–30 days) induces obesity, insulin resistance, hyperandrogenism and the presence of multi-cystic ovaries. This model is particularly interesting to evaluate sub-stances presenting anti-inflammatory, insulin sensitizing or antioxidant effects since it corresponds to a metabolic-PCOS phenotype. Therefore, endocrine and metabolic normalization could be studied using mucoadhesive insitu-gels containing chitosan-fucoidan complexes as bioactive compounds.[57]

Estradiol Valerate-Induced Model (Cystic Ovarian Type)

Estradiol valerate (EV, 4 mg/kg) given intramuscularly in a single dose and its long-lasting effect serves an estrogen induced disturbed follicular maturation and ovarian cyclicity. The animals experience granulosa cell degeneration, anovulation and giant cystic follicles formation. This model is very suitable to study the capability of regeneration of any formulation which can help in folliculogenesis and ovarian tissue restoration since it is employed for studying recovery of structural and morphological features after treatment.[58]

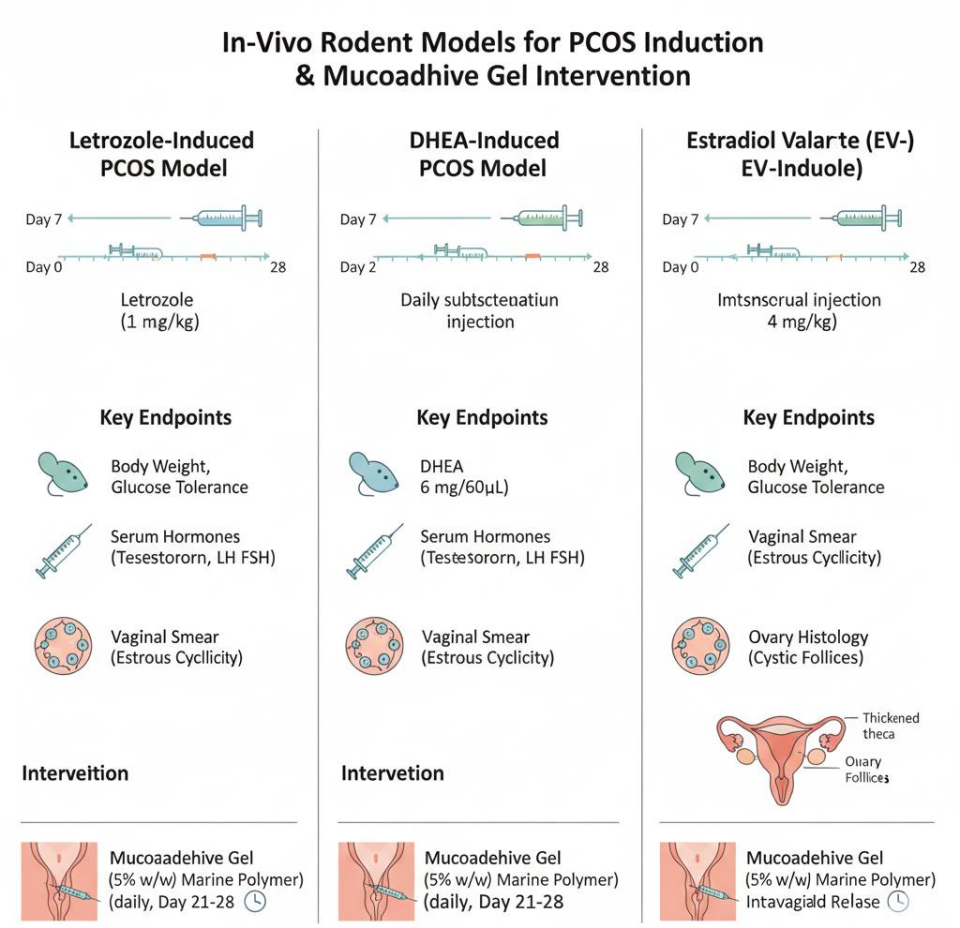

Fig 4: Schematic of In-Vivo Experimental Models for PCOS Key Biomarkers Assessed.

Evaluation across all in-vivo models includes multiple biochemical and histopathological parameters, the major ones being

• Hormonal indicators: including progesterone levels, testosterone, estradiol, FSH, LH, and the LH/FSH ratio.[59]

• Metabolic markers: insulin, HOMA-IR, lipid profile, glucose tolerance, and fasting glucose.[59]

Histological characteristics include presence of corpus luteum, ovarian shape, follicular count and cystic features.[60] Altogether, these indicators make possible the most accurate evaluation of morphological and endocrine recovery achieved under the treatment with the anti-PCOS formulation.[60]

Evaluation Parameters for Mucoadhesive In-Situ Gels

Physicochemical Characterization

Physicochemical properties of mucoadhesive in-situ gels are the majorly impacting factors on their effectiveness, because they influence on gel formation, adhesion and drug release.

• Gelling temperature: It has to be between 35 and 37°C so that after injected it undergoes sol-to-gel transition.

• Viscosity: This factor determines the mechanical strength of the gel and ease of administration; appropriate viscosity ensures good spreadability and staying in contact with skin.

• pH: It must be suited to the site of administration for prevention of stimulation and physical irritation (e.g. vaginal pH 4.0-4.5).

• Mucoadhesion Strength: Determined through shear studies or texture analysers, a high mucoadhesion guarantees an extended residence time of the therapeutic agent on the site of interest.[61,62]

Drug Release and Stability Studies

The drugs release from the gel matrix and its diffusion rate and mechanism can be determined by carrying out in-vitro drug release studies. The release patterns of these formulations generally obey the Higuchi or Korsmeyer-Peppas models related to controlled release kinetics. Stability tests are used to confirm that the formulation behaves as expected during its shelf life in terms of factors such as chemical stability with regard to drug–polymer interactions (using FTIR, DSC), storage stability, and absence of microbial growth.[61]

Pharmacodynamic Assessments

Qualitative measurements such as those obtained in pharmacodynamic evaluations in animal models which provide direct evidence of the intended biological effect of the drug.

• Ovarian Morphology: Corpus luteum reappears and cystic follicles decrease.

• Hormonal Profile: LH/FSH ratio normalization and estrogen/testosterone balance restoration.

• Oxidative Stress Markers: increased activities of catalase (CAT) and superoxide dismutase (SOD) and decreased levels of malondialdehyde (MDA).

These results confirmed the therapeutic efficacy, site-specific targeting and sustained release of mucoadhesive in-situ gels for treatment of PCOS.[60]

Challenges and Future Perspectives in Marine-Derived Therapies and Mucoadhesive Gels for PCOD/PCOS

Management of polycystic ovarian disorder/syndrome (PCOD/PCOS) can be significantly improved by integrating bioactives from marine resources within mucoadhesive in-situ gel systems. Nevertheless, several scientific, technological, and regulatory hurdles limit the translation of these modalities from bench-to-bedside. Future therapeutics that are sustainable, patient-compliant, and competent would be realized when obstacles are recognized with a focus on the therapeutic strategies.[61,62]

CHALLENGES

Limited Clinical Translation

Commercialisation of marine based biomaterials is an expensive and slow process. Despite promising preclinical results, few have progressed beyond clinical evaluation; currently only a very small number of marine derived chemicals have been approved for use in humans (including polysaccharides, carotenoids and peptides). Numerous variables contribute to the disparity between laboratory success and human use, including species variability, lack of long term toxicity studies, lack of bioavailability studies and the regulatory challenges surrounding the sourcing and standardisation of marine biomaterials. Often extraction on a large scale and subsequent clinical translation are hindered or postponed by ethical considerations around conservation of marine biodiversity.[63]

Standardization and Purification Challenges

The animal type, habitat, season and extraction conditions etc. factor in the composition of marine extracts which are inherently comprised of complex mixture of bio-molecules. One of the major challenges among these is to maintain/ensure quantitatively uniform active ingredients and batch-to-batch consistency. Such reproducible and scalable isolation of bio-actives demand sophisticated purification techniques, as membrane filtration, chromatographic isolation, supercritical CO_2 extraction and in absence of such standardization it also becomes difficult to obtain regulatory clearance or compare research outcomes with other studies impacting therapeutic consistency finally.[64]

Stability and Bioavailability Issues

Astaxanthin, fucoidan, and marine peptides are just some of the bioactives derived from marine sources which are chemically unstable, highly susceptible to oxidation enzyme degradation or with very low aqueous solubility. Being rapidly cleared and poor penetrators of biological membranes even further compromise the effectiveness these agents. Therefore, safe delivery systems need to be established such as mucoadhesive in-situ gels that can entrap, stabilise and control release of these labile molecules at their site of action leading to increase in local as well as systemic bioavailability.[65]

Formulation and Scalability of Mucoadhesive Gels

It requires a sophisticated formulation design to develop mucoadhesive in-situ gels that integrate the features of controlled drug release, mucoadhesion, mechanical strength, and optimum gelation. Therefore, appropriate selection and crosslinking of polymers like chitosan, alginate and gellan gum which are often used along with stabilizers, and penetration enhancers to maintain a delicate balance among these properties are necessary. In addition, commercialization problems which include process repeatability, storage stability, and sterility as well as regulatory affairs could potentially cause performance issues of products when scaling-up laboratory-based formulations to industrial scales/production.[66]

Need for Combinational Approaches

PCOS is a complex syndrome with metabolic, inflammatory and endocrine dysfunctions. Considering the fact of its complexity, single-agent therapy will not be sufficient. Complementary combinational therapy also needed to synergize marine bioactives with new polymeric matrices or combined with phytochemicals.[53] or even traditional medications. For instance, fucoidan's antioxidant property combined with chitosan mucoadhesion and permeation-enhancing effect will form multifunctional gel which can stimulate metabolic function by reduce oxidative stress as well as hormone regulatory effect.[54] The holistic approach required for PCOS management can be aptly fulfilled through such hybrid systems.[67]

FUTURE PERSPECTIVES

Personalized and Targeted Therapy

Developments in PCOS genomic, proteomic, and metabolomic profiling are opening the door to more individualized treatment strategies. Mucoadhesive gels made from marine sources could be personalized to an individual's specific inflammatory, metabolic, or hormonal

profile. Personalized formulations might improve both patient outcomes and therapeutic precision via site-specific delivery (eg, nasal for systemic hormone regulation or intravaginal for ovarian modulation).[64]

Biodegradable and Sustainable Polymers

Research on biodegradable polymers produced from marine sources, such as chitin, alginate, or carrageenan, is also gaining interest due to the increasing market demands of environmentally friendly biomaterials. Besides ensuring biocompatibility and low toxicity, these materials will be in line with green pharmaceutical production processes. For example, long-term safety, environmental impact and regulatory approval of future formulations could all possibly be improved by using synthetic or biodegradable marine analogs.[67]

Hybrid and Smart Formulations

A concept anticipated by the researchers is that the next generation of drug delivery systems will be based on hybrid architectures, combing synthetic smart polymers (eg. poloxamers, poly(N-isopropylacrylamide), or nanoparticulate carriers with marine polysaccharides. Stimuli responsive systems respond to physiological triggers such as pH, temperature or ionic strength in a designed manner and provide targeted tissue accumulation, on-demand drug release and hence better therapeutic performance. With these designs mucoadhesive gels can be developed as dynamic platforms for precision medicine.[66]

Clinical Validation and Regulatory Pathways

Products sourced from marine organisms require extensive clinical validation to ensure their successful translation. To ascertain the safety, pharmacokinetics, pharmacodynamics and therapeutic efficacies in patients of PCOS, high quality RCT's are necessary. The development, approval and commercialization of marine bioactives will gain momentum when unified regulatory frameworks can be implemented which address issues ranging from sustainable sourcing to toxicity testing and labelling.[64]

Industrial Scale-Up and Sustainable Production

Overcoming obstacles related to resource sustainability, batch repeatability and economic manufacturing will be crucial for successful commercialization of marine-derived therapeutics. Large scale production must incorporate quality control measures that do not compromise the environment if we hope to meet the demands of patients worldwide. As we look forward, we see that technological advances such as automatically generated gel systems

for in vitro culturing, 'green' (environmentally-friendly) extraction methods biomimicry and/or genetic modification may all play key roles within our future industry. In order to get there quickly enough though regulatory bodies need be working together alongside companies so as not impede progress already being made by perfecting current practices.

CONCLUSION

Among the striking merits of mucoadhesive in-situ gel systems including prolonged residence, sustained release, improved bioavailability transformed them to a potential system for the delivery of drugs locally and controlled release basis. These systems results sol-gel transformation in situ dependent on physiological needs like temperature, pH or ionic strength thus patient compliancy and therapeutic effectiveness are improved. Their mucosal tissues intimate contact is guaranteed by their mucoadhesive nature which decreases drug clearance and allows acting at the target site. This assumes significance when it comes to diseases such as polycystic ovarian disease/syndrome (PCOD/PCOS) where hormonal and metabolic management need to be localized.

The potential of these delivery systems has been further enhanced by incorporation of marine derived polymers especially chitosan, alginate and carrageenan. These biopolymers derived from marine species renewable in nature possess inherent bioactivity and are also characterized by remarkable mucoadhesive, biodegradability and biocompatibility properties. They provide various gelation mechanisms (pH-, ion- and thermo-responsive) thereby facilitating customized formulation design dependent upon applications such as oral, nasal, buccal or intravaginal. Marine bioactives like fucoidan, astaxanthin, marine peptides when encapsulated into these gels provide heightened stability, controlled release and synergistic therapeutic effect against oxidative stress, inflammation and hormonal imbalance associated with PCOS.

Important information about the drugs efficacy of these formulations can be achieved through experimental evaluation using in-vitro and in-vivo models such as granulosa cell cultures, insulin resistant cell lines and animal models induced by letrozole, DHEA, or estradiol valerate. Therapeutic efficacy is supported by LH/FSH ratio, testosterone, insulin resistance and ovarian morphology which are the response indicators. On the other side formulation dependability is assured by physical-chemical analysis (gelation temperature, viscosity) and mucoadhesion studies.

Notwithstanding notable advancements, the sector still confronts translational obstacles pertaining to the scalability, standardization, and purification of components derived from marine sources as well as a dearth of clinical evidence. Important obstacles still include stability, bioavailability, and production consistency. But new developments like hybrid smart gels, biodegradable polymers, and customized formulas have a lot of potential to help get beyond these obstacles.

To conclude, marine-derived mucoadhesive in-situ gel solutions offer a new, sustainable and patient-centric approach for the treatment of PCOD/PCOS. Their capacity to integrate targeted drug delivery, bioactivity, and polymer science at the edge of current knowledge is in coherence with the emerging demand for safety, effectiveness and environmental friendliness. In order to move these concepts from scientific proof-of-concept to clinical practice will require continuing interdisciplinary research, clinical testing, and technological developments that potentially may change reproductive health care forever.

REFERENCES

1. Meng, Y., Zhao, T., Zhang, R., Zhu, X., Ma, C., & Shi, Q. (2025). Global burden of polycystic ovary syndrome among women of childbearing age, 1990–2021; A systematic analysis using the Global Burden of Disease Study 2021. *Frontiers in Public Health, 13*: 1514250. https://doi.org/10.3389/fpubh.2025.1514250
2. Salari, N., Nankali, A., Ghanbari, A., Jafarpour, S., Ghasemi, H., Dokaneheifard, S., & Mohammadi, M. (2024); Global prevalence of polycystic ovary syndrome in women worldwide: a comprehensive systematic review and meta-analysis. *Archives of gynecology and obstetrics*, *310*(3): 1303–1314. https://doi.org/10.1007/s00404-024-07607-x
3. Shukla A, Rasquin LI, Anastasopoulou C. Polycystic Ovarian Syndrome, [Updated 2025 Jul 7]; In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459251/
4. Chen, X., Wan, Y., & Xie, L. (2025). Insulin resistance in polycystic ovary syndrome: Pathophysiological mechanisms of menstrual dysfunction and evidence-based treatment strategies. *Biology of Reproduction, ioaf197.* https://doi.org/10.1093/biolre/ioaf197
5. Li, W., Liu, C., Yang, Q., Zhou, Y., Liu, M., & Shan, H. (2022); Oxidative stress and antioxidant imbalance in ovulation disorder in patients with polycystic ovary syndrome. *Frontiers in Nutrition, 9*, Article 1018674. https://doi.org/10.3389/fnut.2022.1018674

6. Attia, G. M., Almouteri, M. M., & Alnakhli, F. T. (2023); Role of Metformin in Polycystic Ovary Syndrome (PCOS)-Related Infertility. *Cureus*, *15*(8): e44493. https://doi.org/10.7759/cureus.44493
7. Manzoor, S., Ganie, M. A., Amin, S., & et al. (2019); Oral contraceptive use increases risk of inflammatory and coagulatory disorders in women with polycystic ovarian syndrome: An observational study. *Scientific Reports*, *9:* 10182. https://doi.org/10.1038/s41598-019-46644-4
8. Yuan, J., Li, Z., Yu, Y., Wang, X., & Zhao, Y. (2025). Natural compounds in the management of polycystic ovary syndrome: a comprehensive review of hormonal regulation and therapeutic potential. *Frontiers in nutrition*, *12*: 1520695. https://doi.org/10.3389/fnut.2025.1520695
9. Sen, J., Pillai, S., Gopkumar, P., & Sridevi, G. (2014); Formulation and evaluation of muco-adhesive in-situ gel for site-specific delivery of clotrimazole. *GRY Institute of Pharmacy, Borawan, Khargone, India.*
10. Kulkarni, R., Fanse, S., Lalla, R. V., Morales, D., & Burgess, D. J. (2025); Mucoadhesive in situ forming Gels: Bridging Formulation design and physiological Realities. *International journal of pharmaceutics*, *681*: 125834. https://doi.org/10.1016/j.ijpharm.2025.125834
11. Elbandy M. (2022). Anti-Inflammatory Effects of Marine Bioactive Compounds and Their Potential as Functional Food Ingredients in the Prevention and Treatment of Neuroinflammatory Disorders. *Molecules (Basel, Switzerland)*, *28*(1): 2. https://doi.org/10.3390/molecules28010002
12. Dason, E. S., & Dunaif, A. (2021). Diagnosis and management of polycystic ovarian syndrome. *Canadian Medical Association Journal*, *193*(20): E751–E758. https://doi.org/10.1503/cmaj.231251
13. Bertoldo, M. J., Caldwell, A. S. L., Riepsamen, A. H., Lin, D., Gonzalez, M. B., Robker, R. L., Ledger, W. L., Gilchrist, R. B., Handelsman, D. J., & Walters, K. A. (2019); A hyperandrogenic environment causes intrinsic defects that are detrimental to follicular dynamics in a PCOS mouse model. *Endocrinology*, *160*(3): 699–715. https://doi.org/10.1210/en.2018-00966
14. Purwar, A., & Nagpure, S. (2022); Insulin Resistance in Polycystic Ovarian Syndrome. *Cureus*, *14*(10): e30351. https://doi.org/10.7759/cureus.30351

15. Houston, E. J., & Templeman, N. M. (2025). Reappraising the relationship between hyperinsulinemia and insulin resistance in PCOS. *The Journal of endocrinology*, *265*(2): e240269. https://doi.org/10.1530/JOE-24-0269
16. Mohammadi M. (2019). Oxidative Stress and Polycystic Ovary Syndrome: A Brief Review. *International journal of preventive medicine*, *10*: 86. https://doi.org/10.4103/ijpvm.IJPVM_576_17
17. Deng, H., Chen, Y., Xing, J., Zhang, N., & Xu, L. (2024). Systematic low-grade chronic inflammation and intrinsic mechanisms in polycystic ovary syndrome. *Frontiers in immunology*, *15*: 1470283. https://doi.org/10.3389/fimmu.2024.1470283
18. Saadia Z. (2020). Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non- Obese Women. *Medical archives (Sarajevo, Bosnia and Herzegovina)*, *74*(4): 289–293. https://doi.org/10.5455/medarh.2020.74.289-293
19. Sanchez-Garrido, M. A., & Tena-Sempere, M. (2020). Metabolic dysfunction in polycystic ovary syndrome: Pathogenic role of androgen excess and potential therapeutic strategies. *Molecular metabolism*, *35*: 100937. https://doi.org/10.1016/j.molmet.2020.01.001
20. Shi, M., Li, X., Xing, L., Li, Z., Zhou, S., Wang, Z., Zou, X., She, Y., Zhao, R., & Qin, D. (2024). Polycystic Ovary Syndrome and the Potential for Nanomaterial-Based Drug Delivery in Therapy of This Disease. *Pharmaceutics*, *16*(12): 1556. https://doi.org/10.3390/pharmaceutics16121556
21. Wang, K., & Li, Y. (2023); Signaling pathways and targeted therapeutic strategies for polycystic ovary syndrome. *Frontiers in endocrinology*, *14*: 1191759. https://doi.org/10.3389/fendo.2023.1191759
22. Iervolino, M., Lepore, E., Forte, G., Laganà, A. S., Buzzaccarini, G., & Unfer, V. (2021); Natural Molecules in the Management of Polycystic Ovary Syndrome (PCOS): An Analytical Review. *Nutrients*, *13*(5): 1677. https://doi.org/10.3390/nu13051677
23. Thakur, N., & Singh, B. (2025). Designing marine-derived carrageenan-based biomimetic functional materials via a green approach for sustainable development: Cellular proliferation and mucosal tissue drug delivery applications. *RSC Sustainability, 3*: 4598–4621. https://doi.org/10.1039/D5SU00412H
24. Cheng, X., & He, B. (2022); Clinical and Biochemical Potential of Antioxidants in Treating Polycystic Ovary Syndrome. *International journal of women's health*, *14*: 467–479. https://doi.org/10.2147/IJWH.S345853

25. Papadopoulou, S. N. A., Adamantidi, T., Kranas, D., Cholidis, P., Anastasiadou, C., & Tsoupras, A. (2025). A Comprehensive Review on the Valorization of Bioactives from Marine Animal By-Products for Health-Promoting, Biofunctional Cosmetics. *Marine drugs*, *23*(8): 299. https://doi.org/10.3390/md23080299
26. Kouchak M. (2014). In situ gelling systems for drug delivery. *Jundishapur journal of natural pharmaceutical products*, *9*(3): e20126. https://doi.org/10.17795/jjnpp-20126
27. Gözcü, S., & Polat, K. H. (2023); Thermosensitive *In situ* Gelling System for Dermal Drug Delivery of Rutin. *Turkish journal of pharmaceutical sciences*, *20*(2): 78–83. https://doi.org/10.4274/tjps.galenos.2022.00334
28. Cook, M. T., & Kolawole, O. (2023); In situ gelling drug delivery systems for topical drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, *184*: 36–49. https://doi.org/10.1016/j.ejpb.2023.01.007
29. Chatterjee, B., Amalina, N., Sengupta, P., & Mandal, U. K. (2017); Mucoadhesive polymers and their mode of action: A recent update. *Journal of Applied Pharmaceutical Science*, *7*(5): 195–203. https://doi.org/10.7324/JAPS.2017.70533
30. Grabovac, V., Guggi, D., & Bernkop-Schnürch, A. (2005); Comparison of the mucoadhesive properties of various polymers. *Advanced drug delivery reviews*, *57*(11): 1713–1723. https://doi.org/10.1016/j.addr.2005.07.006
31. Vlad, R. A., Pintea, A., Pintea, C., Rédai, E. M., Antonoaea, P., Bîrsan, M., & Ciurba, A. (2025); Hydroxypropyl Methylcellulose-A Key Excipient in Pharmaceutical Drug Delivery Systems. *Pharmaceutics*, *17*(6): 784. https://doi.org/10.3390/pharmaceutics17060784
32. Ramadan, A. A., Elbakry, A. M., Esmaeil, A. H., & Khaleel, S. A. (2018); Pharmaceutical and pharmacokinetic evaluation of novel rectal mucoadhesive hydrogels containing tolmetin sodium. *Journal of pharmaceutical investigation*, *48*(6): 673–683. https://doi.org/10.1007/s40005-017-0365-1
33. Kar, S., & Sanchita, S. (2015); Clomiphene citrate, metformin or a combination of both as the first line ovulation induction drug for Asian Indian women with polycystic ovarian syndrome: A randomized controlled trial. *Journal of human reproductive sciences*, *8*(4): 197–201. https://doi.org/10.4103/0974-1208.170373
34. Thapa, R., Gurung, S., Parat, M. O., Parekh, H. S., & Pandey, P. (2022); Application of Sol-Gels for Treatment of Gynaecological Conditions-Physiological Perspectives and Emerging Concepts in Intravaginal Drug Delivery. *Gels (Basel, Switzerland)*, *8*(2): 99. https://doi.org/10.3390/gels8020099

35. Singh, R. M., Kumar, A., & Pathak, K. (2013); Mucoadhesive in situ nasal gelling drug delivery systems for modulated drug delivery. *Expert opinion on drug delivery*, *10*(1): 115–130. https://doi.org/10.1517/17425247.2013.746659
36. Gilhotra, R. M., Ikram, M., Srivastava, S., & Gilhotra, N. (2014): A clinical perspective on mucoadhesive buccal drug delivery systems. *Journal of biomedical research*, *28*(2): 81–97. https://doi.org/10.7555/JBR.27.20120136
37. Kumar, R., Islam, T., & Nurunnabi, M. (2022); Mucoadhesive carriers for oral drug delivery. *Journal of controlled release: official journal of the Controlled Release Society*, *351*: 504–559. https://doi.org/10.1016/j.jconrel.2022.09.024
38. Irimia, T., Dinu-Pîrvu, C. E., Ghica, M. V., Lupuleasa, D., Muntean, D. L., Udeanu, D. I., & Popa, L. (2018). Chitosan-Based In Situ Gels for Ocular Delivery of Therapeutics: A State-of-the-Art Review. *Marine drugs*, *16*(10): 373. https://doi.org/10.3390/md16100373
39. Gianani, P., Kurup, N., & Rajnani, N. (2025); Emerging applications of marine-derived polymers in targeted drug delivery: A comprehensive review of sources, structures, and pharmaceutical potentials. *Journal of Drug Delivery and Therapeutics*.
40. M Ways, T. M., Lau, W. M., & Khutoryanskiy, V. V. (2018); Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. *Polymers*, *10*(3): 267. https://doi.org/10.3390/polym10030267
41. Amin, M. K., & Boateng, J. S. (2022); Enhancing Stability and Mucoadhesive Properties of Chitosan Nanoparticles by Surface Modification with Sodium Alginate and Polyethylene Glycol for Potential Oral Mucosa Vaccine Delivery. *Marine drugs*, *20*(3): 156. https://doi.org/10.3390/md20030156
42. Hu, C., Lu, W., Sun, C., Zhao, Y., Zhang, Y., & Fang, Y. (2022); Gelation behavior and mechanism of alginate with calcium: Dependence on monovalent counterions. *Carbohydrate Polymers, 294*: 119788. https://doi.org/10.1016/j.carbpol.2022.119788
43. Hu, C., Lu, W., Mata, A., Nishinari, K., & Fang, Y. (2021); Ions-induced gelation of alginate: Mechanisms and applications. *International Journal of Biological Macromolecules, 177*: 578–588. https://doi.org/10.1016/j.ijbiomac.2021.02.086
44. Jabeen, F., Zil-E-Aimen, Ahmad, R., Mir, S., Awwad, N. S., & Ibrahium, H. A. (2025); Carrageenan: structure, properties and applications with special emphasis on food science. *RSC advances*, *15*(27): 22035–22062. https://doi.org/10.1039/d5ra03296b
45. Geonzon, L. C., Descallar, F. B. A., Du, L., Bacabac, R. G., & Matsukawa, S. (2020); Gelation mechanism and network structure in gels of carrageenans and their mixtures

viewed at different length scales – A review. *Food Hydrocolloids, 108*: 106039. https://doi.org/10.1016/j.foodhyd.2020.106039

46. Reys, L. L., Silva, S. S., Soares da Costa, D., Rodrigues, L. C., Reis, R. L., & Silva, T. H. (2023); Building Fucoidan/Agarose-Based Hydrogels as a Platform for the Development of Therapeutic Approaches against Diabetes. *Molecules (Basel, Switzerland)*, *28*(11): 4523. https://doi.org/10.3390/molecules28114523
47. Venkatesan, J., Bhatnagar, I., & Kim, S. K. (2014); Chitosan-alginate biocomposite containing fucoidan for bone tissue engineering. *Marine drugs*, *12*(1): 300–316. https://doi.org/10.3390/md12010300
48. Kraithong, S., Theppawong, A., Liu, Y., Sangsawad, P., & Huang, R. (2025); Fucoidan as an encapsulant material: Applications and advantages in active agents and probiotic encapsulations. *Food Chemistry, 477*: 143570. https://doi.org/10.1016/j.foodchem.2025.143570
49. D'Orazio, N., Gammone, M. A., Gemello, E., De Girolamo, M., Cusenza, S., & Riccioni, G. (2012); Marine bioactives: pharmacological properties and potential applications against inflammatory diseases. *Marine drugs*, *10*(4): 812–833. https://doi.org/10.3390/md10040812
50. Chelu, M., & Musuc, A. M. (2023); Polymer Gels: Classification and Recent Developments in Biomedical Applications. *Gels (Basel, Switzerland)*, *9*(2): 161. https://doi.org/10.3390/gels9020161
51. Thapa, R., Gurung, S., Parat, M. O., Parekh, H. S., & Pandey, P. (2022); Application of Sol-Gels for Treatment of Gynaecological Conditions-Physiological Perspectives and Emerging Concepts in Intravaginal Drug Delivery. *Gels (Basel, Switzerland)*, *8*(2): 99. https://doi.org/10.3390/gels8020099
52. Yudhani, R. D., Sari, Y., Nugrahaningsih, D. A. A., Sholikhah, E. N., Rochmanti, M., Purba, A. K. R., Khotimah, H., Nugrahenny, D., & Mustofa, M. (2023); *In Vitro* Insulin Resistance Model: A Recent Update. *Journal of obesity*, *2023*: 1964732. https://doi.org/10.1155/2023/1964732
53. Lu, L., Li, X., Lv, L., Xu, Y., Wu, B., & Huang, C. (2022); Associations between omega-3 fatty acids and insulin resistance and body composition in women with polycystic ovary syndrome. *Frontiers in nutrition*, *9*: 1016943. https://doi.org/10.3389/fnut.2022.1016943
54. Jung, W., Choi, H., Kim, J., Kim, J., Kim, W., Nurkolis, F., & Kim, B. (2023); Effects of natural products on polycystic ovary syndrome: From traditional medicine to modern drug discovery. *Heliyon, 9*(9): e20889. https://doi.org/10.1016/j.heliyon.2023.e20889

55. Parvini Kohnehshahri, M. (2024); Chitosan/alginate-loaded *Astragalus hamosus* shows ameliorating effects on lipid profile, inflammatory and hormonal parameters, and reduces miRNA-222 expression in polycystic ovary. *Endocrine Abstracts*, *99*: EP226. https://doi.org/10.1530/endoabs.99.EP226
56. Xu, J., Dun, J., Yang, J., Zhang, J., Lin, Q., Huang, M., Ji, F., Huang, L., You, X., & Lin, Y. (2020); Letrozole Rat Model Mimics Human Polycystic Ovarian Syndrome and Changes in Insulin Signal Pathways. *Medical science monitor : international medical journal of experimental and clinical research*, *26*: e923073. https://doi.org/10.12659/MSM.923073
57. Wu, H., Zhao, B., Yao, Q., & Kang, J. (2023); Dehydroepiandrosterone-induced polycystic ovary syndrome mouse model requires continous treatments to maintain reproductive phenotypes. *Journal of ovarian research*, *16*(1): 207. https://doi.org/10.1186/s13048-023-01299-8
58. Venegas, B., De León Gordillo, L. Y., Rosas, G., Espinoza, J. A., Morán, C., Domínguez, R., & Morales-Ledesma, L. (2019); In rats with estradiol valerate-induced polycystic ovary syndrome, the acute blockade of ovarian β-adrenoreceptors improve ovulation. *Reproductive biology and endocrinology: RB&E*, *17*(1): 95. https://doi.org/10.1186/s12958-019-0539-y
59. Ryu, Y., Kim, S. W., Kim, Y. Y., & Ku, S. Y. (2019); Animal Models for Human Polycystic Ovary Syndrome (PCOS) Focused on the Use of Indirect Hormonal Perturbations: A Review of the Literature. *International journal of molecular sciences*, *20*(11): 2720. https://doi.org/10.3390/ijms20112720
60. Huffman, A. M., Rezq, S., Basnet, J., & Romero, D. G. (2023); Biomarkers in Polycystic Ovary Syndrome. *Current opinion in physiology*, *36*: 100717. https://doi.org/10.1016/j.cophys.2023.100717
61. Basu, S., & Bandyopadhyay, A. K. (2010); Development and characterization of mucoadhesive in situ nasal gel of midazolam prepared with Ficus carica mucilage. *AAPS PharmSciTech*, *11*(3): 1223–1231. https://doi.org/10.1208/s12249-010-9477-x
62. Kurniawansyah, I. S., Sopyan, I., Wathoni, N., Fillah, D. L., & Praditya, R. U. (2018); Application and characterization of in situ gel. *International Journal of Applied Pharmaceutics*, *10*(6): 34–37. https://doi.org/10.22159/ijap.2018v10i6.28767
63. Iervolino, M., Lepore, E., Forte, G., Laganà, A. S., Buzzaccarini, G., & Unfer, V. (2021); Natural Molecules in the Management of Polycystic Ovary Syndrome (PCOS): An Analytical Review. *Nutrients*, *13*(5): 1677. https://doi.org/10.3390/nu13051677

64. Malik, S., Saeed, S., Saleem, A., Khan, M. I., Khan, A., & Akhtar, M. F. (2024); Alternative treatment of polycystic ovary syndrome: pre-clinical and clinical basis for using plant-based drugs. *Frontiers in endocrinology*, *14*: 1294406. https://doi.org/10.3389/fendo.2023.1294406
65. Adelakun, S. A., Ukwenya, V. O., Peter, A. B., Siyanbade, A. J., & Akinwumiju, C. O. (2022); Therapeutic effects of aqueous extract of bioactive active component of *Ageratum conyzoides* on the ovarian-uterine and hypophysis-gonadal axis in rat with polycystic ovary syndrome: Histomorphometric evaluation and biochemical assessment. *Metabolism Open*, *15*: 100201. https://doi.org/10.1016/j.metop.2022.100201
66. Chelu, M., & Musuc, A. M. (2023); Polymer Gels: Classification and Recent Developments in Biomedical Applications. *Gels (Basel, Switzerland)*, *9*(2): 161. https://doi.org/10.3390/gels9020161
67. Iervolino, M., Lepore, E., Forte, G., Laganà, A. S., Buzzaccarini, G., & Unfer, V. (2021); Natural Molecules in the Management of Polycystic Ovary Syndrome (PCOS): An Analytical Review. *Nutrients*, *13*(5): 1677. https://doi.org/10.3390/nu13051677
68. Hoang, T. H., Liang, Q., Luo, X., Tang, Y., Qin, J. G., & Zhang, W. (2022); Bioactives from marine animals: Potential benefits for human reproductive health. *Frontiers in Marine Science*, *9*: 872775. https://doi.org/10.3389/fmars.2022.872775.