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Emerging Molecular Targets for Bioactive Molecules in Contraception and Gynecological Disorders: Pharmacological and Translational Perspective

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Abstract

Contraception and gynecological disorders are major areas of unmet therapeutic need in reproductive medicine. Although hormonal contraceptives and conventional pharmacological treatments have improved reproductive health significantly, due to adverse effects, contraindications, adherence, recurrence and effects on fertility, it has been necessary to search for more targeted molecular treatments. Recent research in reproductive biology has identified molecular targets in gamete interaction, sperm motility, steroidogenesis, ovulation, endometrial receptivity, inflammation, angiogenesis, cellular proliferation, apoptosis and metabolic regulation. In contraception, sperm-specific proteins and ion channels such as epididymal protease inhibitor (EPPIN), calcium channel of sperm (CatSper), soluble adenylyl cyclase, sperm-specific sodium/hydrogen exchanger and retinoic acid receptor alpha are emerging as promising targets for non-hormonal approaches.

These pathways will allow for new bioactive molecules to be developed which have higher specificity and less systemic toxicity. At the female gamete level, zona pellucida protein 2 (ZP2) is one of the new targets for preventing sperm-oocyte interactions. In gynecology, estrogen and progesterone receptors, cyclooxygenase-2/prostaglandin pathways, NF-κB, PI3K/AKT, AMPK, TGF-β/SMAD, Wnt/β-catenin, VEGF and oxidative stress pathways are emerging as pharmacologically relevant targets. Natural bioactive molecules such as curcumin, resveratrol, quercetin, epigallocatechin gallate, berberine, ginsenosides, flavonoids and various others can interact with many of these pathways simultaneously. Most of the evidence is still preclinical and there are still challenges in terms of bioavailability, target selectivity, pharmacokinetics, reproductive safety, standardization and clinical validation. This review discusses emerging molecular targets for bioactive molecules in contraception and major gynecological disorders and is focused on molecular mechanisms, pharmacological opportunities and translational challenges. Multi-omics, molecular docking, artificial intelligence, targeted drug delivery and biomarker-based clinical development may enable the transition of promising bioactive molecules from experimental observations to clinically useful reproductive therapeutics.

Keywords: Bioactive molecules; contraception; molecular targets; reproductive health; endometriosis; polycystic ovary syndrome; uterine fibroids; phytochemicals; non-hormonal contraception; translational pharmacology.

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Introduction

Reproductive health is defined by the ways of birth control, fertility, pregnancy planning and disease prevention and treatment of disorders that affect the female and male reproductive systems. Contraception is a critical part of reproductive health because it allows individuals and couples to decide how many and when to have children. In 2021, an estimated 1.1 billion women of reproductive age had a need for family planning, including approximately 164 million women with an unmet need for contraception [1]. Current contraceptive options are hormonal methods, intrauterine devices, barrier methods, permanent sterilization and emergency contraception. These methods are effective but individual responses, contraindications, adverse effects, adherence requirements and concerns around long-term use are all driving new approaches [1,2].

Female hormonal contraceptives have been known to interfere with ovulation through the suppression of the hypothalamic-pituitary-ovarian axis and cervical mucus and endometrial physiology. Hormonal contraceptives have proven beneficial in clinical practice but systemic exposure to steroid hormones can have adverse effects and may not be suitable for some individuals. Furthermore, hormonal birth control is mainly the pharmacological load of women. So, non-hormonal contraceptive approaches for highly targeted reproductive purposes is also an important goal in reproductive pharmacology [2,3] today - the development of non-hormonal contraceptive strategies for women.

Besides contraception, gynecological diseases such as endometriosis, polycystic ovary syndrome (PCOS), uterine fibroids, abnormal endometrial disease and reproductive dysfunction are also profoundly linked by molecular mechanisms. Hormonal imbalance, chronic inflammation, oxidative stress, uncontrolled cellular proliferation, angiogenesis, metabolic dysfunction, altered immune responses and epigenetic changes all contribute to disease onset and progression. Consequently, drugs that target only one physiological endpoint cannot fully address these complex disorders.

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Bioactive molecules are especially relevant here, since they contain multitarget pharmacological activity. Natural compounds such as polyphenols, flavonoids, alkaloids, terpenoids and other secondary metabolites are able to control inflammatory signaling, oxidative stress, steroidogenesis, apoptosis, angiogenesis and metabolic pathways. Recent reviews have shown that there is great interest in natural compounds for endometriosis, PCOS and uterine fibroids, although the majority of evidence comes from cell cultures and animal models [4-8].

So molecular targeting has moved the focus of reproductive pharmacology from nonspecific suppression to selective modulation of pathways that are required to produce fertility and disease progression. In the context of contraception, the objective is to disrupt a key reproductive event such as spermatogenesis, sperm motility, sperm-oocyte interaction or fertilization without producing generalized endocrine disruption. In gynecological disorders, the objective is to suppress pathological estrogen signaling, inflammatory mediators, aberrant growth pathways, oxidative stress or metabolic dysfunction while maintaining physiological reproductive functions.

This review considers novel molecular targets for bioactive molecules in contraception and gynecological disorders, their biological importance, pharmacological mechanisms, potential natural-product modulators and translational opportunities.

Molecular basis of Contraception and opportunities for Targeted Pharmacology

Contraception can theoretically be achieved by interfering with gametogenesis, gamete transport, sperm motility, sperm capacitation, acrosome reaction, sperm-oocyte binding, implantation or early embryonic development. Today contraceptive drug discovery is focused on targets that are essential for reproduction but have limited expression in non-reproductive tissues. Such reproductive selectivity is particularly desirable for non-hormonal contraceptives as it may reduce systemic endocrine effects.

In men, spermatogenesis is mediated by the hypothalamic-pituitary–gonadal axis, while sperm maturation and fertilization is mediated by a

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number of highly specialized proteins and ion channels. Sperm-specific and sperm-enriched proteins have been identified in both genetics and pharmacology for targets including CatSper, soluble adenylyl cyclase (sAC), sperm-specific Na+/H+ exchanger, EPPIN, GAPDHS, PP1γ2 and other proteins (3,9).

In females, contraceptive targeting can be focused on ovulation, oocyte maturation, zona pellucida integrity, sperm-oocyte recognition and endometrial receptivity. The zona pellucida, in particular ZP2, has been much discussed in recent years and the interaction of sperm with ZP proteins is essential in fertilization. Recently, an antibody-derived fragment targeting ZP2 has been demonstrated to prevent fertilization in vitro, demonstrating the potential of ZP2-based non-hormonal contraceptive [10].

Emerging Molecular Targets in Non-Hormonal Contraception.

CatSper Calcium Channel

CatSper is a sperm-specific calcium channel located in the main part of the sperm flagellum and plays a critical role in calcium influx and hyperactivated sperm motility. Sperm hyperactivation is necessary for the efficient passage through the female reproductive tract and penetration into the zona pellucida [9]. Thus, inhibition of CatSper can potentially immobilize sperm without reducing testosterone production or affecting systemic endocrine pathways [9].

CatSper's pharmacological value is that it has very limited reproductive activity. Molecules that are capable of blocking CatSper-mediated calcium release could theoretically lead to rapid-onset, non-hormonal contraception. However, species differences in CatSper pharmacology, ligand specificity and the ability to show complete and reversible CatSper-mediated calcium release in humans remain significant challenges.

Natural products offer an extensive chemical space for screening against sperm ion channels. Alkaloids, terpenoids, polyphenols and other structurally diverse molecules may alter membrane-associated signaling and ion homeostasis. However, there is no direct evidence to demonstrate selective CatSper inhibition by clinically useful natural molecules, and future studies should distinguish nonspecific sperm toxicity from genuine target-mediated effects.

Soluble Adenylyl Cyclase

Soluble adenylyl cyclase is another important sperm-specific target. Like transmembrane adenylyl cyclases, sAC reacts with bicarbonate and calcium and contributes to cyclic AMP production during sperm activation. cAMP signaling modulates protein phosphorylation, motility and capacitation. Pharmacological inhibition of sAC can therefore interfere with essential sperm functions without influencing circulating reproductive hormones [9].

The sAC pathway is particularly attractive for rapid-onset contraception because sperm function can be inhibited after ejaculation. Targeted sAC inhibitors have thus become a key component of non-hormonal male contraceptive research.

EPPIN and Sperm Surface Proteins

EPPIN is a sperm surface protein that interacts with semenogelin and controls the function of sperm. In our results, we have shown that the disruption of EPPIN can lead to reversible contraceptive effects in our experiments. The protein is therefore a potential target for the production of small molecules, peptides or antibody-based contraceptive drugs [11,12].

The EPPIN strategy represents a significant conceptual leap in that it focuses on sperm surface interactions rather than systemic hormonal suppression. Bioactive molecules that are able to disrupt EPPIN-semenogelin interactions or alter EPPIN-associated sperm signaling could be a potential path toward male contraception.

Retinoic Acid Receptor Alpha

Retinoic acid signaling is essential for normal spermatogenesis. Retinoic acid receptor alpha (RARα) is one of the most advanced molecular targets for non-hormonal male contraception. Inhibition of RARα interferes with the retinoic acid-dependent processes of germ cell differentiation and spermatogenesis.

YCT-529 is an example of a selective RARα antagonist engineered through medicinal chemistry and structure-activity optimization. In trials, sperm production and fertility were reduced in rats [13]. However, in a first-in-human phase 1a study, single oral doses of up to 180 mg were found not to positively affect reproductive

hormones, mood or sexual desire and contraceptive efficacy was not established [14].

This study demonstrates the translational value of molecularly validated reproductive targets. It also demonstrates the distinction between target validation, preclinical contraceptive efficacy and clinical proof of contraceptive effectiveness.

Zona Pellucida Protein 2

ZP2 is a major component of the zona pellucida around the mammalian oocyte and contributes to sperm-oocyte recognition. The identification of ZP2 as a potential contraceptive target is particularly interesting because it could prevent fertilization without hormonal suppression [10].

The recent structural studies of ZP2-targeting antibodies have given us a better understanding of ligand-target interactions and how structural biology can assist in the development of next-generation contraceptive molecules. Future strategies may include antibodies, antibody fragments, peptides or small molecules that selectively target the sperm binding regions of ZP2.

Table 1: Major emerging molecular targets and bioactive strategies in contraception and gynecological disorders

Molecular target/pathway	Reproductive or pathological role	Representative bioactive/pharmacological strategy	Major therapeutic opportunity
CatSper	Sperm calcium influx and hyperactivated motility	Selective ion-channel inhibitors; natural-product screening	Non-hormonal male contraception
sAC	cAMP generation, capacitation and sperm motility	sAC inhibitors and structure-based drug design	Rapid-onset non-hormonal contraception
EPPIN	Sperm surface interaction with semenogelin	Small molecules, peptides and immunological approaches	Inhibition of sperm function
RARα	Retinoic-acid-dependent spermatogenesis	Selective RARα antagonists such as YCT-529	Reversible suppression of sperm production
ZP2	Sperm–oocyte recognition	Antibody fragments, peptides and small molecules	Female non-hormonal contraception
ERα/ERβ	Estrogen signaling and endometriotic growth	Selective receptor modulators and phytochemicals	Endometriosis
COX-2/PGE2/EP2/EP4	Inflammation, survival and angiogenesis in endometriosis	COX-2 and EP receptor modulation; polyphenols	Endometriosis and pelvic pain
NF-κB/Nrf2	Inflammation and oxidative stress	Curcumin, quercetin, resveratrol and related compounds	Endometriosis and PCOS
PI3K/AKT/AMPK	Insulin signaling, metabolism and cellular survival	Berberine, curcumin, flavonoids and metabolic modulators	PCOS
TGF-β/SMAD	Fibrosis and extracellular matrix accumulation	EGCG, curcumin and pathway inhibitors	Uterine fibroids
MED12/HMGA2-associated pathways	Fibroid initiation and growth	Molecularly targeted and epigenetic approaches	Uterine leiomyoma
VEGF/angiogenesis	Lesion vascularization	Anti-angiogenic phytochemicals	Endometriosis and fibroids

Bioactive Molecules and Molecular Targets in Endometriosis.

Endometriosis is a chronic, estrogen-dependent inflammatory disorder that is characterized by endometrial-like tissue outside of the uterine cavity. It is associated with chronic pelvic pain, dysmenorrhea, dyspareunia and infertility. The current standard therapies are hormonal or surgical but the recurrence and treatment limitations lead to the need for molecular approaches [15,16].

Estrogen Receptor Signaling

Estrogen signaling is one of the main drivers of endometriotic lesion survival. Both ERα and ERβ are important to disease biology, but ERβ expression is more elevated in inflammatory signaling and progesterone resistance. Abnormal estrogen signaling promotes proliferation, survival, angiogenesis and inflammatory mediator production [15,17]. Natural bioactive molecules may interfere with estrogen biosynthesis and signaling through a variety of mechanisms. Curcumin, resveratrol, quercetin and related polyphenols have been found to affect steroidogenic pathways, inflammatory mediators and cell proliferation in experimentally studied models [18-20] but their effects should not be considered to be equivalent to selective estrogen receptor antagonism because many natural molecules act through multiple targets.

Progesterone receptor and progesterone resistance

Progesterone resistance is a serious therapeutic problem in endometriosis. Low progesterone receptor activity, particularly in PR-B, is associated with lower decidualization and estrogen-dependent inflammation. Molecular mechanisms include altered receptor expression, epigenetic changes, inflammatory cytokines and microRNAs [21]. The therapeutic implication is that bioactive molecules should not simply suppress estrogen but may need to restore progesterone responsiveness. Agents that modulate receptor expression, epigenetic regulation or downstream progesterone signaling could be a more physiologically balanced strategy.

COX-2–PGE2–EP2/EP4 Signaling

Prostaglandin E2 is involved in endometriosis-associated inflammation, estrogen biosynthesis, angiogenesis and cellular survival. PGE2 binds to EP1/EP4 receptors with EP2 and EP4 signaling associated with ERK1/2, AKT, NF-κB and β-catenin pathways [22]. Targeting EP2 and EP4 inhibits endometriotic cell survival and adhesion experiments have been reported [22,23]. This pathway is a particularly attractive molecular bridge between inflammation and hormonal signaling. Thus, polyphenolic molecules with COX-2 inhibitory, antioxidant and NF-κB-modulating properties may have multitarget activity against endometriotic lesions.

NF-κB and Oxidative stress

Inflammation and oxidative stress are linked mechanisms in endometriosis. Activated macrophages, cytokines and reactive oxygen species are involved in lesion formation, angiogenesis and pain. NF-κB is an important transcriptional regulator of inflammatory mediators.

There is widespread interest in curcumin because the experimental evidence suggests that it can interact with NF-κB, COX-2 inflammatory cytokines, oxidative stress, angiogenesis and cell apoptosis [19,20]. Resveratrol and quercetin also affect oxidative and inflammatory pathways. A systematic review of curcumin, quercetin and resveratrol reported beneficial effects in inflammation, oxidative stress, proliferation, invasion, adhesion, apoptosis and angiogenesis of the human body but clinical evidence is insufficient to make definitive therapeutic conclusions [20].

Angiogenesis and VEGF

Endometriotic lesions require vascularization to continue to grow. VEGF and associated angiogenic pathways are thus attractive targets. Biologically active compounds with anti-angiogenic properties may reduce lesion formation by reducing endothelial growth, migration and vascular permeability.

Curcumin, epigallocatechin-3-gallate and flavonoids have been found to be anti-angiogenic agents in animal experiments [18-20]. The translational challenge is to have sufficient local concentrations at endometriotic lesions without causing any undesirable systemic anti-angiogenic effects.

Bioactive molecules and molecular targets for polycystic ovarian syndrome

PCOS is a heterogeneous endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Insulin resistance, hyperinsulinemia, obesity, chronic low-grade inflammation, oxidative stress and altered hypothalamic–pituitary–ovarian signaling often coexist with the reproductive abnormalities [24].

Insulin Receptor–IRS–PI3K/AKT Signaling

Insulin resistance is among the most important metabolic disorders of PCOS. Binding of insulin to its receptor activates insulin receptor substrate proteins and downstream PI3K/AKT signaling. Alteration of this pathway can impair glucose transport and metabolic homeostasis and indirectly contribute to ovarian androgen excess [25].

Bioactive molecules such as berberine, curcumin, inositols and several flavonoids have been investigated for their ability to improve insulin sensitivity and modulate PI3K/AKT signaling. Natural compounds can regulate IR/IRS-1, PI3K/AKT, AMPK, NF-κB and Nrf2 pathways and provide a mechanistic basis for their potential effects on both metabolic and reproductive abnormalities [26].

AMPK as Metabolic/ Reproductive Target

AMPK is an intracellular energy sensor and regulates glucose and lipid metabolism. AMPK activation can improve insulin sensitivity and suppress excessive anabolic signaling. Therefore, AMPK regulation of metabolism can affect ovarian steroidogenesis and follicular development.

The application of AMPK to reproductive disorders has stimulated the search for metformin and natural AMPK-modulating compounds. Bioactive molecules that affect AMPK may offer complementary approaches for correcting metabolic disturbances in PCOS, especially when combined with lifestyle and established pharmacological interventions.

Oxidative stress and Nrf2.

Oxidative stress leads to ovarian dysfunction, insulin resistance and chronic inflammation in PCOS. Nrf2 is a common transcription factor that is involved in antioxidant defense. Bioactive compounds like polyphenols could enhance endogenous antioxidant pathways and reduce oxidative damage by Nrf2-related pathways [26,27].

This mechanism is very relevant to the development of multi-target phytopharmaceuticals because antioxidant activity alone may be insufficient, whereas simultaneous modulation of oxidative stress, inflammation and metabolic signaling may provide broader therapeutic benefit.

Steroidogenic Enzymes and Hyperandrogenism

Ovarian androgen excess is associated with increased activity of steroidogenic enzymes including CYP17A1 and CYP11A1 and altered androgen receptor signaling. Biogenic molecules that can regulate steroidogenesis may decrease androgen production and promote follicular maturation.

Recent reviews have identified natural compounds that influence CYP17A1, CYP19A1 and other steroidogenic targets, but the evidence differs widely between compounds and experimental models [28]. Therefore, mechanistic findings should be validated using human ovarian tissue, clinically relevant concentrations and pharmacokinetic studies.

Wnt/β-Catenin, TGF-β and Hippo/YAP Pathways

PCOS is now increasingly recognized as a systems-level disorder involving multiple signaling networks. PI3K/AKT, TGF-β/SMAD, Wnt/β-catenin and Hippo/YAP pathways influence follicular development, granulosa-cell function, fibrosis, cellular proliferation and metabolic regulation [29]. These pathways offer rational screening of bioactive molecules. Rather than choosing compounds based on their antioxidant activity, future drug discovery could focus on compounds with sufficient ability to correct defined molecular abnormalities at once.

Bioactive Molecules and Molecular Targets in Uterine Fibroids

Uterine fibroids or leiomyomas are benign tumors of uterine smooth muscle that produce heavy menstrual bleeding, pelvic pain, anemia, infertility and pregnancy-related complications. Their biology is heavily influenced by estrogen and

progesterone signaling, extracellular matrix accumulation and genetic abnormalities [30].

Progesterone Receptor Signaling

Progesterone plays an important role in fibroid development and growth. Progesterone receptors can stimulate proliferation, inhibit apoptosis, increase cytokine production and increase extracellular matrix accumulation. Progesterone signaling is also linked to Wnt, growth factor and inflammatory pathways [31].

So, selective modulation of progesterone receptor signaling is an important pharmacological strategy. Natural compounds can complement this approach by affecting inflammatory and proliferative pathways associated with progesterone action.

MED12 and Genetic Drivers

Somatic mutations in MED12 are one of the most common molecular abnormalities in uterine fibroids. MED12-associated alterations have been shown to affect transcriptional regulation and cell signaling, including cyclin-dependent kinase activity and AKT signaling [30,32].

The MED12 and HMGA2 abnormalities have opened the door to looking at fibroids not as hormone-dependent lesions but rather as a molecularly heterogeneous disease. Future bioactive-molecule discoveries could then be targeted at molecules that can modulate mutant-associated signaling rather than simply lower levels of hormone in the body.

TGF-β/SMAD and Extracellular Matrix

Excessive extracellular matrix deposition is a characteristic of fibroids. TGF-β signaling can trigger fibroblast activation, collagen deposition and tissue remodeling through SMAD-dependent pathways. If targeted, fibroid growth and stiffness may be decreased.Epigallocatechin gallate, vitamin D, curcumin and other natural compounds have been studied in experimental fibroid models because of their effects on proliferation, fibrosis, oxidative stress and extracellular matrix regulation [33,34]. However, clinical evidence remains insufficient to establish these agents as alternatives to standard therapies.

Bioactive Molecules in Other Gynecological and Reproductive Disorders

The molecular targets described above are not restricted to specific diseases. Inflammation, oxidative stress, hormonal signaling, insulin resistance and altered apoptosis generally overlap with gynecological disorders. This overlap offers a reason for multitarget pharmacology.

For example, endometrial dysfunction may result from interactions between estrogen/progesterone signaling, inflammatory pathways, oxidative stress and altered cellular proliferation. Curcumin has been extensively studied in endometriosis and other endometrial disorders because it can play a role in inflammatory, oxidative, angiogenic and proliferative mechanisms [35].

Metformin is another example of pathway-oriented pharmacology. Although it is not a naturally bioactive compound, its effects on AMPK, PI3K/AKT, IGF signaling, MAPK and NF-κB illustrate how one pharmacological molecule can influence several interconnected pathways relevant to PCOS and other gynecological disorders [36].

Vaginal and reproductive tract disorders also involve epithelial barrier function, immune signaling and microbial interaction. Future studies may therefore focus on bioactive molecules that modulate host-microbiome interactions as opposed to conventional antimicrobial activity. Such approaches might be particularly relevant to recurrent reproductive tract conditions in which microbial dysbiosis and inflammatory responses coexist.

Natural Bioactive Molecules as Leads for Contraceptive Drug Discovery

Natural products have historically been involved in pharmacological discovery, and reproductive pharmacology is an example of this. Gossypol, a polyphenolic compound from cotton, had been found to be a significant antifertility agent in men but was not a safe contraceptive for a number of reasons such as hypokalemia and incomplete reversibility [37,38]. Gossypol affects sperm energy metabolism, mitochondrial function and ATP-dependent processes, indicating both the potential and risk of natural antifertility agents [39].

Neem-based preparations have also been extensively studied for contraceptive and antifertility effects. Experimental evidence has been provided on spermatogenesis, sperm function, ovulation and reproductive tissues, but mechanistic heterogeneity and insufficient clinical

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validation prevent translation into an established contraceptive therapy [40].

A systematic review of the natural products with potential for non-hormonal male contraception revealed many compounds with potential against sperm function. β-caryophyllene, embelin, oleanolic acid, triptonide and N-butyldeoxynojirimycin were identified as promising targets for further investigation on the basis of the efficacy, safety and reversibility of these compounds [41].

These examples show that natural products should not simply be considered traditional remedies. They represent chemically diverse molecular libraries that can be used for target identification, lead optimization and structure-based drug discovery. And, at the same time, historical examples such as gossypol show that strong biological activity does not necessarily translate into a clinically acceptable contraceptive.

Pharmacological optimization and drug delivery strategy

The major limitation of many natural bioactive molecules is not necessarily lack of biological activity but poor pharmacokinetic performance. Curcumin, resveratrol, quercetin and a number of flavonoids exhibit low solubility in aqueous solutions, fast metabolism and low systemic bioavailability. As a result, concentrations in cell culture may not be achievable in human tissues after conventional oral administration.

Nanotechnology-based delivery systems can address some of these limitations. Liposomes, polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, phytosomes and targeted hydrogel systems can improve solubility, stability and tissue exposure. Local delivery may be particularly attractive for gynecological disorders because therapeutic concentrations could potentially be achieved at reproductive tissues while reducing systemic exposure.

However, for the delivery of contraception, the delivery needs depend on the molecular target. For example, a sperm-targeting molecule that must be rapidly delivered and then accumulated in the reproductive tract may need systemic exposure, or a vaginal or cervical contraceptive to be delivered in the local area. Likewise, an intrauterine delivery system could provide long-term exposure to a uterine target and minimize systemic hormonal effects.

The formulation of targeted formulations should be driven by target biology, not by formulation technology alone. Pharmacokinetic-pharmacodynamic modeling, tissue distribution studies and reproductive toxicology should be considered in formulation optimization.

Translational Perspective: From Molecular Target to Clinical Candidate

Importantly, translation of bioactive molecules from experimental research to clinical practice takes several steps. Target validation should first indicate that the target acts to achieve a reproducible biological effect and that the target is causally relevant to fertility or disease. Genetic knockout, CRISPR-based studies, pharmacological inhibition and rescue experiments can serve as complementary evidence.

For contraceptive targets, reversibility is particularly important. A candidate should ideally deliver reliable contraceptive efficacy without permanent reproductive damage. Studies can then look at recovery of spermatogenesis, ovarian function, fertility, offspring development and reproductive tissue integrity after drug withdrawal.

Another major consideration is species specificity. We have shown how reproductive proteins and ion channels are significantly different in humans and in other animal models. A compound that is very effective in mice may have less activity against the human orthologue. Human sperm and organoid models, ex vivo reproductive tissues and humanized models should be incorporated into the animal studies.

Recent advances in male contraception demonstrate such translational progress. Sperm-specific targets like CatSper, sAC and EPPIN have been identified through molecular and genetic studies, and antagonism of RARα has been developed for clinical investigation [9,13,14].

In female contraception, ZP2 is another way in which structural biology is applied to define a reproductive target and develop selective binding molecules [10]. These approaches demonstrate the potential for molecular pharmacology to be combined with structural biology, computational chemistry and biologics development.

The role of multi-Omics and artificial intelligence in Target Discovery

The complexity of reproductive disorders makes conventional single-target drug discovery increasingly inadequate. Transcriptomics, proteomics, metabolomics, epigenomics and single-cell sequencing can identify molecular signatures of disease progression and treatment response. Integrating these datasets could reveal previously unrecognized targets.

Artificial intelligence could accelerate this process by finding relationships among molecular targets, bioactive compounds and disease phenotypes. Machine-learning models can then select compounds according to the predicted binding affinity, toxicity, bioavailability and pathway activity. Molecular docking and molecular dynamics can then provide structural information on ligand-target interactions.

For PCOS, transcriptomic data integration with machine learning techniques has been proposed to find potential biomarkers and molecular pathways. These approaches could lead to biomarker-guided treatments and help to predict patients that are likely to respond to specific bioactive compounds [42].

The same strategy can be applied to endometriosis by integrating lesion transcriptomics, inflammatory profiles, estrogen receptor expression and treatment-response data. In fibroids, integration of MED12/HMGA2 status with steroid receptor expression and extracellular matrix signatures could help to classify patients for targeted interventions.

Safety, Reproductive Toxicology and Regulatory Considerations.

The development of reproductive therapeutics requires a particularly rigorous safety framework because the target population could include healthy individuals of reproductive age. For contraceptives, the acceptable therapeutic window must be sufficiently broad to ensure reliable efficacy without affecting systemic endocrine function, sexual health, future fertility or offspring health.

Natural origin does not necessarily imply safety. Gossypol is an excellent example of a natural compound with high antifertility activity yet poor safety and reversibility [37,38]. Complex herbal extracts may contain multiple constituents with different concentrations, so standardization is difficult.

For gynecological disorders, the reproductive status of the patient must also influence treatment development. A compound that removes endometriotic lesions but permanently erodes ovarian reserve would have a fundamentally different clinical value from a compound that suppresses disease while preserving fertility.

So standardization is very important. Bioactive molecules should be characterized chemically, measured and quantified in a well-characterized way using a validated analytical procedure and assessed for impurities, metabolites and batch-to-batch variability. Pharmacokinetic parameters such as absorption, distribution, metabolism, elimination and tissue penetration should be associated with pharmacodynamic biomarkers.

Future reproductive pharmacology will move towards highly selective, mechanism-based and personalized interventions. For contraception, sperm-specific targets such as CatSper, sAC, EPPIN and RARα may provide non-hormonal approaches and ZP2 may be a promising female-specific target. These targets offer us the opportunity to screen natural product libraries, synthetic compounds and biologics using target-based and phenotypic approaches.

For gynecological disorders, the most promising approach is pathway-oriented rather than disease-oriented. Endometriosis can be managed through estrogen/progesterone signaling, PGE2, NF-κB, oxidative stress and angiogenesis. PCOS

can be controlled through insulin signaling, AMPK, PI3K/AKT, steroidogenesis, inflammation and oxidative stress. Fibroids can be treated by progesterone signaling, MED12-related pathways, TGF-β/SMAD, extracellular matrix remodeling and stem cell biology.

Future clinical development should distinguish between compounds for disease treatment and compounds to be complementary nutraceuticals. The pharmacological criteria for these applications are different. Therapeutic claims need to be supported by adequate evidence regarding dose, exposure, efficacy, safety and mechanism. The combination of artificial intelligence, molecular docking, high-throughput screening, metabolomics, transcriptomics, single-cell analysis and advanced drug-delivery systems could considerably accelerate discovery. Phenotypic screening is particularly valuable because it can be used to identify compounds that can alter cellular functions in complex cellular systems, even if the exact molecular target is not known. Phenotypic screening of human sperm has already been shown as a useful method in identifying compounds that are contraceptive-active [43].

The most important translation objective is therefore not just to identify more bioactive compounds, but to establish a complete chain of evidence connecting chemical structure, molecular target, cellular mechanism, pharmacokinetics, tissue exposure, therapeutic efficacy and safety.

Conclusion

These molecular targets are changing how contraceptive and gynecological therapeutics are discovered from a reliance on a single hormonal or nonspecific therapeutic target towards more selective and mechanism-based pharmacology. CatSper, sAC, EPPIN, RARα and ZP2 targets are promising targets for non-hormonal contraception, and estrogen and progesterone receptors, COX-2/PGE2, NF-κB, PI3K/AKT, AMPK, Nrf2, TGF-β/SMAD, VEGF and MED12-related pathways are also important targets in gynecological disease.

Bioactive molecules, especially natural polyphenols, flavonoids, terpenoids and alkaloids, are in great potential since they are able to regulate multiple biological pathways simultaneously. Studies have demonstrated the action of compounds such as curcumin, resveratrol, quercetin, EGCG, berberine, cumin, and other phytochemicals on endometriosis, PCOS and uterine fibroids. The present evidence should be taken very cautiously because most of it is preclinical and there is no direct comparison between dose, formulation, experimental models and outcome measures.

Future development of these agents will entail robust target validation, human-relevant models, pharmacokinetic optimization, reproductive toxicology, standardized formulations and well-designed clinical trials. Combining multi-omics, artificial intelligence, structure-based drug design and targeted delivery with respect to the development of bioactive drugs could lead to improved efficacy and safety. And finally, molecular pharmacology and translational reproductive medicine will lead to a new generation of contraceptives and gynecological therapeutics that are more selective, reversible, personalized and compatible with long-term reproductive health.

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