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Original Article

The Role of Delayed-Release Butyrate as an Adjuvant Therapy in Modulating Primary Metabolic Regulation in PCOS to Address Metabolic Dysfunction and Endocrine Disorders

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ABSTRACT

PCOS is a complex endocrine–metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and low-grade chronic inflammation, significantly impacting reproductive, metabolic, and cardiometabolic health in women of reproductive age. Gut dysbiosis, particularly reduced populations of SCFA producing bacteria, including butyrate, contributes to increased intestinal permeability, LPS translocation, activation of TLR4-NFκB inflammatory pathways, and impaired insulin signaling, exacerbating insulin resistance, hyperandrogenism, and ovarian phenotype. This review aimed to evaluate delayed-release butyrate as an adjuvant therapy in PCOS through modulation of primary metabolic pathways via the gut-brain-ovary axis, intestinal barrier enhancement, and local ovarian immunomodulation. Literature search was performed in PubMed, Web of Science, Science Direct, Elsevier, and Google Scholar using keywords combining PCOS, butyrate, delayed-release, gut microbiota, insulin resistance, metabolic dysregulation, with inclusion of articles from the past 10 years assessing SCFA or butyrate on metabolism, inflammation, and ovarian function. Results indicate that butyrate supplementation, particularly delayed-release formulations, increases local SCFA concentrations in the colon, strengthens tight junctions, suppresses proinflammatory cytokines, reduces endotoxemia, and modulates the gut-brain-ovary axis, improving insulin resistance, reproductive hormone profile, and estrous cyclicity in preclinical models, with support from preliminary clinical data. Compared to standard therapies such as metformin or inositol, butyrate provides a unique mechanism complementing systemic metabolic effects through microbiota modulation, SCFA restoration, and ovarian inflammation regulation. In conclusion, delayed-release butyrate has potential as an adjuvant therapy in PCOS by targeting gut dysbiosis, primary metabolic dysregulation, and local ovarian inflammation, supporting future controlled clinical trials and personalized microbiota-based therapeutic strategies.

Keywords: *Butyrate, Delayed-Release, Dysbiosis, Gut Microbiota, PCOC*

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ABSTRAK

PCOS merupakan gangguan endokrin metabolik kompleks yang ditandai oleh hiperandrogenisme, disfungsi ovulasi, resistensi insulin, dan inflamasi kronis ringan yang berdampak signifikan pada kesehatan reproduktif, metabolik, dan kardiometabolik perempuan usia subur. Disbiosis mikrobiota usus terutama penurunan populasi bakteri penghasil SCFA termasuk butirat berkontribusi terhadap peningkatan permeabilitas usus, translokasi LPS, aktivasi jalur inflamasi TLR4-NFκB, dan gangguan *insulin signaling* yang memperburuk resistensi insulin, hiperandrogenisme, dan fenotipe ovarium. Kajian ini bertujuan menelaah peran butirat *delayed-release* sebagai terapi adjuvan dalam modulasi metabolik primer pada PCOS melalui interaksi *gut-brain-ovary axis*, perbaikan *barrier* usus, dan efek imunomodulator lokal pada ovarium. Metode mencakup penelusuran literatur di *PubMed*, *Web of Science*, *Science Direct*, *Elsevier*, dan *Google Scholar* menggunakan kombinasi kata kunci PCOS, butirat, *delayed-release*, *gut microbiota*, resistensi insulin, disregulasi metabolik, dengan kriteria inklusi artikel 10 tahun terakhir yang menilai SCFA khususnya butirat pada metabolisme, inflamasi, dan fungsi ovarium. Hasil kajian menunjukkan bahwa suplementasi butirat terutama dengan formulasi *delayed-release* dapat meningkatkan konsentrasi lokal SCFA di kolon, memperkuat *tight junction*, menekan sitokin proinflamasi, mengurangi endotoksinemia, serta memodulasi sumbu *gut-brain-ovary* sehingga memperbaiki resistensi insulin, profil hormon reproduktif, siklus estrus pada model preklinis, serta didukung oleh beberapa data klinis awal. Dibandingkan terapi standar seperti metformin atau inositol, butirat menawarkan mekanisme unik yang melengkapi efek metabolik sistemik melalui modulasi mikrobiota, SCFA, dan inflamasi ovarium. Kesimpulannya, butirat *delayed-release* berpotensi sebagai terapi adjuvan pada PCOS dengan menargetkan disbiosis usus, dysregulasi metabolik primer, dan inflamasi lokal ovarium yang membuka arah penelitian lebih lanjut untuk uji klinis terkontrol dan personalisasi terapi berbasis metabolit mikrobiota.

Kata Kunci: *Butyrate, Delayed-Release, Dysbiosis, Gut Microbiota, PCOC*

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a metabolic endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and low-grade chronic inflammation, with broad implications for the health of women of reproductive age. Globally, PCOS prevalence is estimated at 5–10% among women of childbearing age (15–49 years), varying by diagnostic criteria used such as the Rotterdam, National Institutes of Health (NIH), or Androgen Excess Society (AES) criteria.[1] A recent meta-analysis reported a global average prevalence of 9.2%.[1]

In Indonesia, although epidemiological data on PCOS remain limited, several clinical and observational studies suggest a prevalence comparable to global estimates, ranging from 5–10% among women of reproductive age.[2] Based on projections of approximately 74.56 million women aged 15–49, the number of women with PCOS is estimated to fall between 3.73 and 7.46 million.[3] PCOS has also been identified in adolescent populations, with a prevalence of approximately 6.5% among girls aged 15–19, indicating that the syndrome can manifest early in life and carries potential for long-term health consequences.[2]

Beyond its high prevalence, PCOS is associated with an elevated risk of long-term metabolic complications, including insulin resistance, dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease. Observational studies have shown that individuals with PCOS have higher incidence rates of type 2 diabetes and cardiovascular disease compared to controls, even after adjusting for body mass index.[4]

Conventional therapies such as metformin and inositol have been used to address the metabolic aspects of PCOS particularly insulin resistance and menstrual irregularities. Metformin has demonstrated efficacy in reducing insulin resistance and hyperandrogenism, but is frequently accompanied by gastrointestinal side effects, while evidence for inositol's effectiveness on metabolic and reproductive parameters remains inconsistent.[5] These limitations highlight the need for more comprehensive therapeutic approaches that target

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upstream metabolic mechanisms, including primary metabolic dysfunction and systemic inflammation.

In recent decades, the gut microbiota has emerged as an important mediator in PCOS pathogenesis. Scientific evidence indicates that gut microbial dysbiosis contributes to PCOS etiology through metabolic and immunological pathways that influence ovarian function, collectively referred to as the gut–ovary axis.[6] Women with PCOS exhibit a reduction in short-chain fatty acid (SCFA)-producing bacteria, such as those generating butyrate, propionate, and acetate, which play a key role in maintaining intestinal barrier integrity and metabolic regulation.[7]

Among SCFAs, butyrate is a fermentation metabolite produced from dietary fiber by bacteria such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium* spp. It enhances insulin sensitivity through activation of G-protein–coupled receptors (GPR41/43) and modulation of systemic metabolic signaling.[8] Reduced butyrate production in PCOS contributes to increased intestinal permeability, lipopolysaccharide (LPS) translocation, chronic inflammatory activation, and impaired insulin signaling all of which worsen insulin resistance.[6] SCFAs may also influence glucose regulation, energy homeostasis, and the hypothalamic–pituitary–ovarian (HPO) axis, though direct evidence in humans remains limited.[8]

Disrupted microbiota–host interactions are also linked to local ovarian inflammation. Reduced serum butyrate levels have been reported to correlate with increased expression of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in ovarian granulosa cells in PCOS models, while exogenous butyrate supplementation has demonstrated improved inflammatory profiles and epigenetic modifications in animal studies.[9] Taken together, these findings confirm that the gut–ovary axis represents a key pathophysiological pathway linking intestinal dysbiosis, SCFA production, insulin resistance, and ovarian dysfunction in PCOS providing a rational basis for therapeutic strategies targeting gut microbiota modulation and its metabolites.[7]

METHODS

A literature review was conducted using Boolean logic search strategies across scientific databases including PubMed, Web of Science, ScienceDirect, Elsevier, and Google Scholar. A total of 28 references were used. Search terms included combinations of: *"polycystic ovary syndrome" OR "PCOS"*, *"butyrate" OR "short-chain fatty acids"*, *"delayed-release" OR "colon-targeted delivery"*, *"gut microbiota"*, *"insulin resistance"*, and *"metabolic dysregulation"*.

Inclusion criteria encompassed articles relevant to PCOS that evaluated the role of SCFAs, particularly butyrate as therapeutic interventions, including delayed-release delivery approaches, and examined their implications for primary metabolic regulation, insulin resistance, inflammation, and endocrine dysfunction through mechanisms relevant to the gut–ovary axis. Articles were excluded if they addressed PCOS using pharmacological or nutraceutical interventions unrelated to butyrate. The search was limited to journal articles published within the past 10 years to ensure data relevance and currency.

RESULT AND DISCUSSION

Metabolic Pathophysiology of PCOS as a Therapeutic Target

PCOS is a condition that affects not only the reproductive system but also systemic metabolism more broadly. One of its hallmark features is insulin resistance, which occurs when target tissues including muscle, adipose tissue, and the liver fail to respond effectively to insulin, forcing the pancreas to produce greater amounts of insulin (hyperinsulinemia) as compensation. Studies indicate that 50–70% of women with PCOS experience insulin resistance even in the absence of overt obesity, underscoring that insulin resistance is the central metabolic anomaly in PCOS and operates across multiple body tissues.[10]

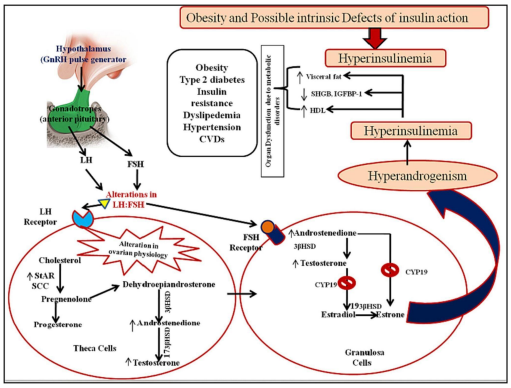

Figure 1. *"The Insulin–Androgen "Vicious Cycle" in PCOS*[11]

Insulin resistance in PCOS also interacts with ovarian endocrine mechanisms. Insulin functions as a co-gonadotropin by amplifying luteinizing hormone (LH) stimulation of ovarian theca cells, thereby increasing androgen synthesis. Furthermore, hyperinsulinemia suppresses hepatic production of sex hormone–binding globulin (SHBG), resulting in elevated free androgen levels and worsening the hyperandrogenic phenotype of PCOS. This reciprocal interaction between insulin resistance and androgen overproduction is referred to as the metabolic–endocrine vicious cycle, in which each condition mutually exacerbates the other.[12]

At the level of the hypothalamic–pituitary–ovarian (HPO) axis, insulin resistance and hyperandrogenism contribute to an increased frequency of gonadotropin-releasing hormone (GnRH) pulses, producing a predominance of LH secretion over follicle-

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stimulating hormone (FSH) and elevating the LH/FSH ratio. This imbalance further amplifies theca cell stimulation, while granulosa cells experience impaired FSH signaling that reduces aromatase (CYP19) activity. As a result, the conversion of androgens to estrogen becomes suboptimal, leading to intraovarian androgen accumulation that inhibits follicular maturation and drives chronic anovulation.[11,12]

Concurrently as illustrated in the figure hyperinsulinemia is also associated with increased visceral adiposity and systemic metabolic dysfunction, including dyslipidemia and reduced high-density lipoprotein (HDL) levels, which further worsen insulin resistance and low-grade inflammation. The reciprocal interaction between insulin resistance and hyperandrogenism forms a metabolic–endocrine vicious cycle in which metabolic dysregulation reinforces hormonal dysfunction and vice versa, confirming that PCOS is a multisystem syndrome rooted in primary metabolic dysregulation.[11,12]

As demonstrated by the reciprocal interactions among hyperinsulinemia, hyperandrogenism, and ovarian dysfunction in the PCOS pathophysiology framework, metabolic and hormonal disturbances do not operate as isolated processes rather, they mutually reinforce one another within an integrated system. The integration of metabolic and endocrine components in PCOS can be understood through the concept that insulin resistance and low-grade inflammation represent components of primary upstream metabolic regulation. These systemic interactions also serve as the initial triggers of dysfunction that give rise to the clinical manifestations of PCOS, including anovulation and hyperandrogenism. Within this framework, metabolic dysregulation forms the foundation upon which hormonal alterations develop making upstream metabolic targets such as insulin sensitivity and systemic inflammation potentially important therapeutic focal points for more effectively intervening in the disease pathway.[13]

Gut Microbiota Dysbiosis and Bacterial Community Alterations in PCOS

Multiple studies have demonstrated that PCOS patients exhibit gut microbiota dysbiosis significant alterations in bacterial composition compared to healthy controls including a reduction in short-chain fatty acid (SCFA)-producing bacteria such as Faecalibacterium prausnitzii, Roseburia, and Eubacterium spp., which are the primary sources of butyrate, as well as an elevated Firmicutes/Bacteroidetes ratio associated with obesity and insulin resistance.[7] This dysbiosis is also more pronounced in PCOS patients with insulin resistance, suggesting that this metabolic condition correlates closely with microbiota alterations even in the absence of overt obesity.[6]

Moreover, while numerous studies have documented gut microbiota dysbiosis in PCOS, it remains debated whether these changes represent a primary cause or a consequence of the condition. Fecal microbiota transplantation (FMT) studies transferring microbiota from PCOS patients into germ-free mice demonstrated induction of ovarian dysfunction, insulin resistance, and metabolic disturbances in recipient animals findings that support an active role for gut dysbiosis in PCOS pathogenesis through metabolic and hormonal modulation.[16] However, metabolic factors inherent to PCOS, such as hyperandrogenism and insulin resistance, may themselves alter microbiota composition. The relationship between PCOS and dysbiosis is therefore bidirectional and complex.[17]

Interindividual variation in microbiota composition is considerable, influenced by genetic factors, diet, metabolic status, and ethnicity. Although reduced populations of SCFA-producing bacteria including *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium* spp. represent a consistent finding, beta-diversity across studies reveals substantial differences in microbial community structure across various populations.[18] This carries important clinical implications, as responses to microbiota-modifying interventions such as probiotics, prebiotics, dietary therapy, or lifestyle modification may vary considerably between individuals. Personalized microbiota-based therapeutic strategies that account for PCOS metabolic subtypes are therefore recommended to optimize clinical outcomes.[19]

The Role of SCFAs in Metabolic Homeostasis

The reduction in SCFA-producing bacteria including *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium* spp. in PCOS patients contributes to gut dysbiosis that is closely associated with insulin resistance and systemic inflammation. SCFAs, including acetate, propionate, and butyrate, are produced through microbial fermentation of dietary fiber and play a critical role in regulating metabolic homeostasis and intestinal epithelial integrity. SCFAs interact with G-protein–coupled receptors (GPR41/43) on enteroendocrine cells, intestinal cells, and pancreatic β-cells to stimulate secretion of hormones such as GLP-1 and PYY, thereby improving glucose regulation and insulin sensitivity.[6,8]

In addition, SCFAs reinforce tight junction proteins within the intestinal epithelium, preventing leaky gut, and activate PPARγ, which supports fatty acid oxidation and modulation of the mucosal immune response collectively suppressing systemic inflammation and insulin resistance. Among SCFAs, butyrate stands out as a key component due to its role in providing energy to colonocytes, strengthening the intestinal barrier, and suppressing inflammation, making it a primary focus in maintaining metabolic homeostasis in conditions such as PCOS.[6]

Leaky Gut, Endotoxinemia, and Chronic Inflammation

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The decrease in butyrate production due to dysbiosis causes increased intestinal permeability (leaky gut) which allows the translocation of pro-inflammatory molecules such as lipopolysaccharide (LPS) into the systemic circulation, thereby activating the TLR4-NFκB pathway, triggering the expression of pro-inflammatory cytokines such as IL-6 and TNF-α which then inhibit insulin signaling and worsen insulin resistance.[6] Clinical models also show that markers of decreased barrier function such as zonulin and LPS are associated with increased inflammation and insulin resistance in PCOS, strengthening the hypothesis that intestinal barrier dysfunction can facilitate a metabolic cascade that triggers and worsens the PCOS phenotype.[6]

The Impact of Dysbiosis on Reproductive Hormone Regulation

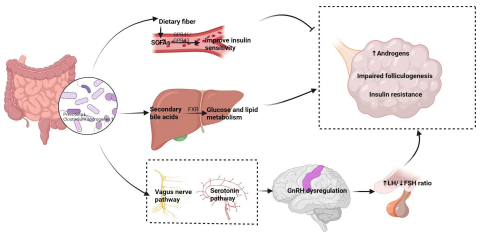

Figure 2. *Pathogenesis Mechanism of PCOS through the Gut Ovary Axis7*

Gut dysbiosis not only affects metabolism but also directly impacts the hormonal system through SCFA modulation. Through activation of the GPR41/43 receptor, SCFAs, including butyrate, regulate the secretion of enteroendocrine hormones that play a role in the hypothalamic-pituitary-ovarian (HPO) axis, influencing the secretion of luteinizing hormone (LH) and androgen, which are key characteristics of PCOS.[10] A decrease in the population of SCFA-producing bacteria and impaired production of these metabolites can exacerbate hyperandrogenism, impair follicular maturation, decrease sensitivity to FSH, and strengthen the hyperinsulinemia-hyperandrogenism feedback loop.[14]

This pathway aligns with the proposed gut-ovarian axis model. As shown in Figure 2, dysbiosis influences PCOS through multiple mechanisms: SCFAs increase insulin sensitivity and suppress ovarian androgen synthesis via GPR41/43; secondary bile acids modulate glucose and lipid metabolism via FXR; and disruption of the gut-brain-ovarian neuroendocrine pathway alters GnRH secretion. These multipathway interactions collectively contribute to hyperandrogenism, insulin resistance, and follicular dysfunction, explaining how gut dysbiosis can be both a trigger and an amplifier of the PCOS phenotype.[7]

Molecular Mechanism of Butyrate in Ovarian Tissue

Mechanistic studies in animal and cellular models have shown that butyrate can exert direct anti-inflammatory effects in ovarian tissue through epigenetic modulation, for example by decreasing the activity of METTL3-mediated m6A methylation in the FOSL2 gene, thereby reducing the expression of inflammatory factors such as IL-6 and TNF-α in ovarian granulosa cells. Butyrate supplementation also improved ovarian morphology and decreased local inflammatory markers in an obese PCOS model, suggesting a direct relationship between SCFAs and the ovarian environment.[9] Meta-analyses of clinical trials have shown that interventions targeting gut microbiota metabolites, such as sodium butyrate administration, probiotics, and synbiotics, can significantly reduce total testosterone, LH/FSH ratio, fasting insulin levels, and HOMA-IR in PCOS women, as well as improve metabolically relevant lipid profiles, supporting the idea that butyrate and SCFA modulation correlate with improvements in two key domains of PCOS: metabolic and hormonal.[15]

Delayed-Release Butyrate as Adjuvant Therapy

The limitations of oral butyrate formulations are a major challenge to its use as a therapeutic agent. Butyrate has high local bioactivity in the colon, but absorption in the proximal gastrointestinal tract and rapid metabolism by the small intestinal epithelium and colonocytes results in most oral butyrate being absorbed before reaching the target site. Consequently, its colonic bioavailability is low, limiting its effectiveness in microbiota modulation and intestinal barrier repair.[20] Conventional unprotected oral formulations release butyrate before it reaches the colon, so the effective dose reaching the biological target is significantly reduced and clinical outcomes are highly dependent on the delivery technology and release profile, not just on the amount of butyrate administered.[21] Consequently, many traditional clinical studies show high variability in therapeutic response, even when relatively large oral doses are administered, because most of the free butyrate is rapidly absorbed in the upper tract and does not reach optimal therapeutic concentrations in the colon.[21]

To address these issues, delayed-release and colonic-targeting formulations have been developed that utilize pH-specific coating systems or microcapsules to delay the release of butyrate until it reaches the terminal ileum and colon. These formulations enhance local absorption in target tissues, allowing butyrate to maintain effective concentrations in the colonic environment without premature degradation in the small intestine. Recent clinical evidence indicates that microcapsules and colonic-release formulations of sodium butyrate (e.g., Butyrose®) significantly increase gut microbiota diversity and alter microbial community composition, as well as reduce abdominal pain in patients with uncomplicated diverticular disease after 90

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days of treatment (400 mg/d) with a favorable safety profile.[22]

Advantages of delayed-release systems include the ability to direct butyrate release directly into the colon, thereby increasing local metabolite concentrations and minimizing undesired early absorption. This approach results in more stable immunomodulatory and metabolic effects through direct interaction with the colonic epithelium and SCFA receptors, such as GPR41/43, which are relevant in conditions of dysbiosis, intestinal inflammation, and metabolic disorders. A recent literature review confirmed that butyrate formulation technology influences clinical outcomes. The colon-release microcapsulated version demonstrated superior efficacy compared to the conventional form, particularly regarding modulation of the microbiota and inflammatory response.[21, 23] Based on this information, delayed-release butyrate can overcome the pharmacokinetic limitations of conventional oral forms and strengthen therapeutic targets in the colon, thus having potential as an adjuvant therapy in conditions involving intestinal dysbiosis, inflammation, and metabolic dysfunction.

Preclinical and Clinical Evidence of Butyrate in PCOS

Preclinical evidence consistently suggests that butyrate can improve various aspects of PCOS pathophysiology through metabolic, inflammatory, and reproductive function modulation. In a letrozole-induced PCOS mouse model, butyrate supplementation was reported to restore paraoxonase-1 (PON-1) function, reduce the degree of hyperinflammation, and improve metabolic and cardiorenal dysfunction associated with PCOS, demonstrating the broad therapeutic effects of this SCFA.[24] Furthermore, sodium butyrate (NaBu) administration to PCOS mice increased colonic butyrate levels, decreased body weight, improved lipid metabolism, and reset the estrous cycle, sex hormone levels, and ovarian phenotype, supporting a role for butyrate in improving reproductive function through the gut-brain-ovary axis.[25]

Initial clinical support also comes from a meta-analysis of probiotic/synbiotic-based intervention trials that included sodium butyrate as a therapeutic component, where these interventions reduced testosterone levels, LH/FSH ratio, fasting insulin levels, and HOMA-IR in women with PCOS, although the number of butyrate-specific studies is still limited and needs to be expanded.[15]

Adjuvant Therapy Approach in PCOS Based on Metabolic Targets

Gut microbiota dysbiosis and SCFA deficits, particularly butyrate, are crucial components in the pathophysiology of PCOS, influencing insulin resistance, ovarian inflammation, and metabolic dysfunction. Adjuvant therapies targeting these microbiota metabolites, such as sodium butyrate (NaBu) in a delayed-release formulation, add a new dimension to PCOS management. Although metformin remains the first-line therapy recommended by international guidelines, adjuvant strategies like butyrate offer unique mechanisms not available to metformin, including direct modulation of the gut-brain-ovary axis, intestinal barrier repair, and local immunomodulatory effects in the ovary.

This comparative table of metabolic therapies for PCOS demonstrates the differences in mechanism and effectiveness between butyrate, inositol, and metformin. In addition to metabolic and hormonal effects, butyrate modulates gut microbiota and SCFA metabolites, which directly influence ovarian inflammation and granulosa cell function through epigenetic regulation (m6A) and activation of GPR41/43 receptors in the colonic epithelium.

These mechanisms allow butyrate to reduce endotoxinemia, strengthen the gut barrier, and suppress proinflammatory cytokines, all of which contribute to improved estrous cycles and reproductive hormone profiles in PCOS models. These preclinical findings confirm that butyrate acts not only as a local energy metabolite but also as a systemic modulator linking gut metabolism, ovarian inflammation, and hormone regulation, opening previously underexplored avenues of mechanistic research. [26, 27]

Inositol has been shown to reduce BMI, testosterone, and glucose, and increase SHBG, but results are heterogeneous and some outcomes are inconsistent compared to metformin.[26] Metformin remains superior for insulin resistance and systemic metabolic parameters, but does not target dysbiosis or SCFA deficits that are important for ovarian inflammation.[27]

Therefore, butyrate has the potential as an adjuvant therapy to complement metabolic and inflammatory pathways not addressed by standard therapy, allowing for strategic combinations that reduce systemic insulin resistance while modulating the gut-brain-ovary axis for improved ovarian function and microbiota balance.

Table 1. *Comparison of Metabolic Therapy in PCOS*

Therapy / Study	Type of Study	Group	Parameters Assessed	Key Results	Notes/ Limitation	Source

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Butyrate – NaBu	Preclinical, animal model	NaBu vs. PCOS Control	⬇ Testosterone, ⬇ Insulin, ⬆ E_2, ⬆ P_4; estrous cycle improvement	Modifies metabolic & reproductive parameters via gut–brain–ovary axis	Animal model only; no human RCT available	[25]
Butyrate – Epigenetik granulosa	Preclinical, human tissue	PCOS vs Control	⬇ Granulosa inflammation via m6A FOSL2	Demonstrates mechanism of inflammation reduction: dysbiosis → ovarian inflammation	No clinical data on dosing or human cohorts	[9]
Inositol – Meta-analisis PCOS	RCT / meta-analysis	Inositol vs Placebo / Metformin	⬇ BMI, ⬇ Testosterone, ⬇ Glucose, ⬆ SHBG	Non-inferior vs. placebo; some outcomes comparable to metformin	Heterogeneous evidence; effects depend on formulation	[26]
Metformin – *Standard therapy*	RCT / guideline review	Metformin vs no metformin	⬇ BMI, ⬇ LDL, ⬇ *Insulin resist,* ⬆ *Pregnancy rate*	First-line therapy for insulin resistance & metabolic dysfunction	Gastrointestinal side effects more frequent	[27]

The role of butyrate as a gut microbiota metabolite has emerged as a potential therapeutic target in the management of PCOS through its ability to improve metabolic regulation and reduce the systemic inflammatory response that contributes to insulin resistance, a key component of PCOS pathophysiology. Butyrate, through its interaction with SCFA receptors such as FFAR2/FFAR3, has been shown to increase enteroendocrine hormone secretion, improving insulin sensitivity and glucose metabolism, and maintaining the integrity of the gut barrier, preventing endotoxin translocation that triggers chronic inflammation. A deeper understanding of the gut-ovary axis and its interactions with genetic factors, dietary patterns, and metabolic comorbidities will provide a strong foundation for more effective and safe personalized therapies.[28]

CONCLUSION

Delayed-release butyrate has emerged as a promising adjuvant therapeutic strategy in PCOS by targeting gut microbial dysbiosis and primary metabolic dysregulation, two key mechanisms underlying insulin resistance, hyperandrogenism, and ovarian dysfunction. Delayed-release formulations increase local colonic bioavailability, strengthen the intestinal barrier, suppress proinflammatory cytokines, and modulate the gut-brain-ovary axis, collectively improving metabolic and hormonal profiles. Preclinical evidence suggests that butyrate can improve ovarian phenotype, reduce granulosa cell inflammation through epigenetic regulation (m6A), and restore the balance of short-chain fatty acids (SCFAs). Clinical data also confirm its potential to safely improve insulin resistance and hormonal parameters.

While metformin remains the gold standard therapy for reducing systemic insulin resistance, butyrate offers an additional mechanism that targets metabolic and inflammatory pathways not addressed by conventional therapies. Thus, delayed-release butyrate functions as a systemic modulator linking gut metabolism, ovarian inflammation, and hormonal regulation. These findings open new perspectives for the development of personalized therapies in PCOS, based on modulating the microbiota and its metabolites.

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SUGGESTION

Based on the conclusions obtained, it is recommended that further research focus on conducting randomized controlled clinical trials to evaluate delayed-release butyrate in women with PCOS, taking into account variations in metabolic phenotype and obesity status. Future studies should assess comprehensive clinical outcomes, including metabolic parameters (e.g., HOMA-IR, lipid profile), hormonal parameters (testosterone, LH/FSH ratio), inflammatory indicators, and ovarian function to ensure meaningful and measurable clinical benefits.

Furthermore, further development of formulation technology that allows selective release of butyrate in the colon is recommended. This formulation approach is expected to increase bioavailability, reduce gastrointestinal side effects, and produce synergistic effects in modulating the gut-ovarian axis, thus providing a more effective and precise therapeutic strategy for PCOS. Multidisciplinary research is also expected to integrate aspects of gut microbiology, endocrinology, pharmacology, and nutritional science to identify biomarkers of response to butyrate-based therapy and develop individualized therapy models tailored to patient characteristics. This approach is expected to strengthen the scientific basis for the use of delayed-release butyrate as an adjuvant therapy and support its rational implementation in future clinical practice.

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