Maturitas 206 (2026) 108830

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

New Investigator Award

Impact of long-term medication on estrobolome-associated β-glucuronidase and sulfatase activities: Implications for estrogen homeostasis in postmenopausal women

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ARTICLE INFO

Keywords:
Menopause
Estrobolome
Long-term medication
β-Glucuronidase
Gut microbiota
Sulfatase

ABSTRACT

Menopause leads to a decline in circulating estrogen levels, increasing cardiometabolic risk, contributing to bone loss, and decreasing quality of life. The estrobolome, a subset of microbes with β-glucuronidase (GUS) and sulfatase activities, regulates estrogen homeostasis through deconjugation and enterohepatic recycling, thereby influencing systemic estrogen availability. Common long-term pharmacological treatments in postmenopausal women may alter gut microbial composition and function, potentially affecting estrobolome activity and systemic estrogen levels.

This narrative review examines current evidence on how long-term pharmacological treatments may affect estrobolome-associated GUS and sulfatase activities, with implications for estrogen metabolism and health outcomes in postmenopausal women. A targeted literature search was performed to identify clinical studies on commonly prescribed drugs for hypertension, diabetes, dyslipidemia, osteoporosis, and depression in postmenopausal women, focusing on microbial taxa with reported GUS or sulfatase activity.

Among the evaluated pharmacological classes, antidiabetic drugs, particularly metformin, are the most extensively studied, followed by antidepressants. These treatments can modulate key gut bacterial genera with GUS and sulfatase activities, including *Bifidobacterium*, *Roseburia*, *Faecalibacterium*, and *Clostridium*, which are relevant to metabolic and estrogen homeostasis. However, no studies have directly assessed the impact of pharmacological treatments on GUS and sulfatase activity in postmenopausal women.

Understanding how chronic medication influences estrobolome dynamics may help identify strategies to support estrogen balance and improve systemic metabolic, hormonal, vascular, and inflammatory profiles. This review highlights the interplay between long-term medication, gut microbiota, and estrogen homeostasis as a promising avenue for personalized microbiota-targeted therapies in postmenopausal health.

1. Introduction

Menopause marks the permanent cessation of menstruation, resulting from the depletion of oocytes and the loss of endogenous gonadal steroids [1–3]. This hormonal shift disrupts various physiological systems, making menopause a critical phase in women's health. Typically, menopause is diagnosed retrospectively, 12 months after the final menstrual period, occurring at an average age of 51, although this varies across geographic and ethnic populations [4,5]. The menopausal transition may be accompanied by several symptoms that vary in severity from woman to woman, including vasomotor symptoms (e.g., hot flashes), genitourinary symptoms such as vaginal atrophy and dryness, mood and sleep changes, and bone loss. Over 80% of women experience symptoms during menopausal transition, with about one-third of them suffering from severe symptoms. These symptoms often begin one to two years before the final menstrual period and may persist for several years after menopause [6]. On average, the menopausal transition can last up to 4 years or more [1].

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https://doi.org/10.1016/j.maturitas.2026.108830
Received 24 November 2025; Received in revised form 2 January 2026; Accepted 6 January 2026
Available online 9 January 2026

Notably, there is evidence showing that severe and persistent vasomotor manifestations are associated with an increased cardiovascular disease (CVD) risk, which is promoted by the decline in estrogen levels. This hormonal decline accelerates endothelial dysfunction and contributes to hypertension, atherosclerosis, and other CVD risk factors.

Another major health concern in postmenopausal women is osteoporosis, as highlighted by the Menopause Society [7]. Bone mineral density begins to decline approximately one year before the final menstrual period and continues to decrease, albeit at a slower rate, for about two years afterward, particularly at the lumbar spine and femoral neck [8,9]. This bone loss is primarily driven by estrogen deficiency.

Estrogens play a pivotal role in cardiovascular health by modulating vascular function, metabolism, and cardiac hypertrophy. They enhance nitric oxide production, inhibit the renin-angiotensin system, and reduce endothelin-1 synthesis by endothelial cells [10,11].

In addition, estrogens improve serum lipid profiles and help lower blood pressure [12], which could promote endothelial vasodilation and influence autonomic regulation. Estrogens are also believed to modulate inflammatory markers, including cytokines [10], which are exacerbated by oxidative stress [13,14]. In contrast, testosterone may induce vasoconstriction and platelet aggregation by upregulating thromboxane A2 receptor expression [15]. Moreover, population studies associate androgens with increased visceral fat accumulation, dyslipidemia, and higher cardiometabolic risk [10].

Another relevant aspect associated with the menopausal transition is the impact of estrogen depletion on the gut microbiome. Women generally have a more diverse gut microbiome than men during early adulthood. However, this difference diminishes with age, likely due to menopause [16]. Higher levels of estrogen and progesterone are associated with greater microbial diversity. In turn, a diverse gut microbiome with high deconjugation activity may enhance hormone retention. However, postmenopausal women show distinct microbiome features, including increased sulfate transport and a tendency toward reduced β-glucuronidase (GUS) activity, contributing to sex hormone retention [16]. In this regard, the estrobolome is a subset of gut microbes enriched in GUS and sulfatase activities, which can deconjugate estrogens for reabsorption into the systemic circulation, thereby playing a key role in estrogen homeostasis [17]. Although certain studies in specific subpopulations, such as postmenopausal women with breast cancer, have reported elevated GUS activity [18], the majority of the evidence supports the notion that menopause-associated gut dysbiosis and inflammation are linked to an overall decline in microbial GUS activity [16,19]. Overall, estrogen deficiency promotes gut dysbiosis (i.e., an imbalance in microbiome composition and functionality) during menopause, thereby impairing gut barrier integrity. This may contribute to microbial component translocation, metabolic endotoxemia, pro-inflammatory status, reduced bone mineral density, and increased CVD risk [20]. Conversely, gut microbiotas enriched in microbes with high GUS activity may contribute to the pathogenesis of estrogen-driven diseases by promoting the recirculation and reactivation of endogenous and exogenous estrogen-like molecules [21].

Given the increased CVD risk associated with aging, exacerbated by menopause, which often requires pharmacological treatment (e.g., lipid-lowering drugs, antihypertensives, and antidiabetics, among others), alongside treatments for osteoporosis, anxiety, and depression, a significant proportion of postmenopausal women are on some form of pharmacological therapy. Notably, it is known that medications can alter the gut microbiota [22], particularly in polymedicated patients, such as those with metabolic syndrome [23].

Therefore, given the importance of the estrobolome in estrogen metabolism, this review explores the potential impact of the main long-term pharmacological treatments commonly used in postmenopausal women on gut microbial GUS and sulfatase activities, and consequently, on systemic estrogen homeostasis.

The aim is to highlight how pharmacological factors can shape gut microbial composition and function and, in turn, influence hormonal homeostasis, cardiometabolic risk, and quality of life during postmenopause.

2. Methods

A targeted literature search was conducted in PubMed, Web of Science, and Scopus up to October 2025 to identify human studies investigating the impact of pharmacological treatments on gut microbiota with GUS and sulfatase activities. The search strategy combined controlled vocabulary (MeSH terms), gut microbiome-related concepts, and major drug classes commonly prescribed to postmenopausal women to prevent cardiometabolic diseases and depression, such as antidiabetic, antihypertensive, lipid-lowering, anti-osteoporotic, antidepressant, and anxiolytic/benzodiazepine drugs.

The following search query was used:

(name of specific bacterial taxa with reported GUS or sulfatase activities) AND (“antidiabetic” OR metformin OR “antihypertensive” OR “angiotensin-converting enzyme inhibitors” OR “angiotensin II receptor blockers” OR “beta-blockers” OR “calcium channel blockers” OR “lipid-lowering” OR statins OR “hypolipidemic” OR “antidepressant” OR SSRI OR SNRI OR “tricyclic antidepressants” OR fluoxetine OR anxiolytic OR benzodiazepines OR diazepam OR “osteoporosis drugs” OR bisphosphonate OR alendronic acid OR ibandronic acid) AND menopause. This initial search for the term “menopause” yielded no results. Therefore, the term “menopause” was replaced by “(humans OR volunteers OR patients)”.

In addition, this review did not include hormone replacement therapy (HRT) because its primary mechanism of action directly modifies circulating estrogen levels rather than altering microbial enzymatic activities. Our focus was on non-hormonal pharmacological treatments that may secondarily influence estrogen metabolism by modulating gut microbiota-mediated GUS and sulfatase activity.

Only peer-reviewed human studies published in English were included. Studies were excluded if they: i) used animal or in vitro models, ii) assessed the combined effects of drugs with probiotics or dietary supplements, or iii) evaluated drug response as a secondary outcome (e.g., comparisons between “responders” and “non-responders” to dietary or probiotic interventions).

Eligible articles were required to provide explicit gut microbiota data, obtained through 16S rRNA sequencing or metagenomics, and to report the direction of taxonomic changes (i.e., increases or decreases in microbial abundance) in response to specific drugs or drug combinations. Reference lists of included articles and relevant reviews were also screened to identify additional publications meeting the inclusion criteria.

3. The estrobolome concept: the significance of glucuronidase activity (GUS)

The gut microbiota has been the subject of exponential research in the last decade. It is now considered one of the key elements contributing to host health regulation [24]. Our aim here is not to enumerate the many processes in which the gut microbiota is involved, including those related to nutrition, immune response, cardiometabolic diseases, neurodegenerative disorders, and cancer, as well as other aspects such as emotions, sleep, mood, and athletic performance, among others.

Although substantial evidence supports the causal role of the gut microbiota in certain processes, much of the evidence linking gut microbiota and many physiological processes is based solely on correlation studies [24]. Clinical and experimental studies support the connection between gut microbiota and the pathophysiology of various diseases. For instance, gut microbiota alterations induced by bariatric surgery have been linked to improvements in several adverse metabolic indicators associated with metabolic syndrome, such as hyperlipidemia

and hypertension [25]. Moreover, bariatric surgery in obese women can reduce the risk of developing endometrial hyperplasia and, subsequently, endometrial cancer [26]. In addition, mounting evidence has shown that infertility and endometriosis are associated with dysbiotic gut microbiota [27].

In the context of breast cancer, impaired gut microbiota may influence carcinogenesis through multiple mechanisms, contributing to adiposity, hormonal imbalances, and immune dysregulation, all of which are key factors in carcinogenesis [28]. These findings highlight the interconnected nature of many chronic diseases and underscore the therapeutic potential of targeting the gut microbiota to achieve clinical benefits across multiple conditions [29–32].

The vast enzymatic arsenal of the human gut microbiota allows the metabolism of xenobiotics, including drugs, pollutants, and plant-derived compounds [33,34]. Although many of the species involved in specific catabolic steps, such as hydrolysis, double bond reductions, dehydroxylations, ring cleavage, and demethylations, are increasingly being identified, most species remain unknown [33,35].

Certain gut microbes, collectively referred to as the "estrobolome", can deconjugate estrogens primarily through β-glucuronidase activity (GUS), and, to a lesser extent, sulfatase, thereby enabling their reabsorption into the systemic circulation [18]. Once deconjugated, estrogens re-enter the bloodstream and bind to estrogen receptors alpha and beta [36] (Fig. 1). A decrease in specific gut bacterial populations in humans, such as that caused by antibiotic use, leads to increased fecal excretion of conjugated estrogens and lower urinary estrogen levels [37]. Focusing on GUS, gut microbial enzymes involved in estrogen deconjugation have historically been annotated under different gene names, although the term "GUS" is the predominantly accepted nomenclature in the literature to refer to microbial β-glucuronidases.

Two genes encoding its activity have been identified in the human gut microbiota, commonly referred to as *BG* and *gus* [38]. *BG*-annotated genes are more prevalent in human gut metagenomes than *gus*-annotated genes [39], with gus sequences mainly associated with Bacillota and BG annotations distributed across both Bacillota and Bacteroidota [38,40].

Importantly, regardless of annotation, GUS constitute a structurally and functionally diverse enzyme family comprising multiple well-defined functional clades, as established through extensive protein structural analyses [41].

Postmenopausal gut dysbiosis is characterized by a diminished Bacillota/Bacteroidota ratio, a reduced abundance of the *Lachnospiraceae* family, and an elevated abundance of the genera *Prevotella*, *Parabacteroides*, *Bacteroides*, and *Bilophila* [42]. Recently, data published by the Human Microbiome Project's GI database reinforces previously described findings. They have developed a human intestinal GUS atlas, identifying about 279 *gus* genes, of which 93.5% are taxonomically classified as Bacteroidota (52%), Bacillota (43%), Verrucomicrobia (1.5%), and Proteobacteria (0.5%) [22].

To date, no studies have directly examined the influence of long-term pharmacological treatments on the modulation of GUS and sulfatase activities (e.g., through inhibition or activation). However, growing evidence indicates that several pharmacological treatments can modulate the abundance and enzymatic potential of specific gut microbial taxa with GUS and sulfatase activities. These microbial shifts can influence drug metabolism, enterohepatic circulation, and systemic bioavailability, potentially affecting both efficacy and toxicity profiles.

4. Impact of long-term medication on the estrobolome

The influence of both intrinsic and extrinsic factors on the composition of the gut microbiome is becoming increasingly understood. Alterations in microbial communities induced by dietary patterns can be as critical as those triggered by pharmacological treatments, since both exogenous factors target microbial taxa involved in estrogen metabolism and redox regulation, which are recognized as key determinants of women's health [18,30,43]. Although most of the available evidence focuses on the profound effects of antibiotic treatments, it is now well established that other widely used medications can also affect gut microbial composition [23,24,44].

To illustrate these relationships, Table 1 summarizes the main gut microbial taxa reported to encode GUS and/or sulfatase activities, and

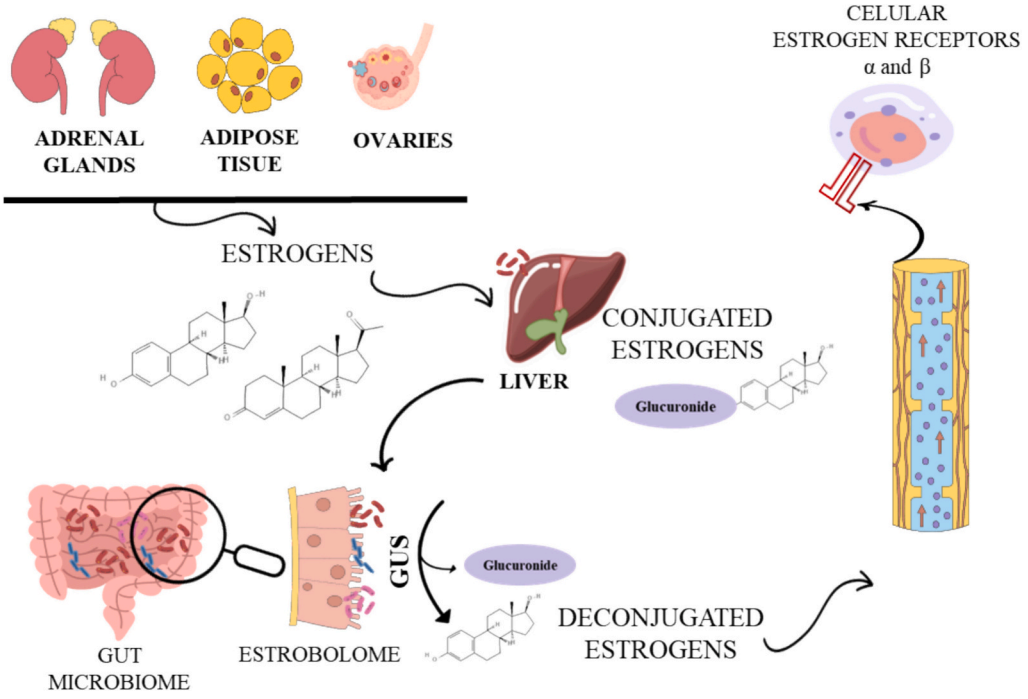

Fig. 1. Estrogens produced by the ovaries, adrenal glands, and adipose tissue are metabolized in the liver, yielding biologically inactive conjugated forms. This inactive estrogen is then deconjugated by gut microbial β-glucuronidase (GUS) and transformed into a biologically active form (deconjugated estrogens), which are reabsorbed into the bloodstream.

Table 1
Effects of commonly prescribed medications, selected based on their frequent use in postmenopausal women, on gut microbial taxa with β-glucuronidase (GUS) and/or sulfatase activity.

Taxa	GUS	Sulfatase	Antidiabetic drugs	Antihypertensives	Antidepressants	Lipid-lowering drugs
Bifidobacterium	[36,45]		↑Abundance in Chinese T2DM patients treated with metformin (n = 130) [46]. ↑Abundance in Mexican adults with prediabetes treated with metformin and linagliptin (n = 167) [47]. ↑Abundance in T2DM patients with non-alcoholic fatty liver disease treated with combined metformin and exenatide treatment vs. metformin alone [48]. ↑Abundance upon α-glucosidase inhibitor treatment in T2DM patients [46].		↓Abundance upon antidepressant medication (SSRIs, TCAs) across three Dutch cohorts (LifeLines-DEEP, 1000IBD, and IBS; total n ≈ 2400 adults) [23]. ↑Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (n = 26) [49].	↑Abundance upon atorvastatin (20 mg/day) in newly diagnosed hypercholesterolemic East Chinese subjects (n = 202) [50].
B. adolescentis	[51]		↑Abundance in obese PCOS women treated with combined metformin and exenatide vs. metformin alone (n = 29) [52].			
B. angulatum	[51]					
B. bifidum	[53]	[54]	↑Abundance in metformin-treated community-dwelling Colombian adults with T2DM [55].			↓Abundance in atorvastatin-treated hypercholesterolemic patients (n = 27), compared with untreated hypercholesterolemic patients (n = 15) and healthy subjects (n = 19) [56].
B. breve	[51,53]	[57]				
B. pseudolongum	[53]					
B. longum	[51,53]		↑Abundance upon α-glucosidase inhibitor treatment in Chinese patients with T2DM [58]. ↑Abundance upon acarbose treatment in Chinese patients with T2DM [58].			↑Abundance upon prior chronic statin use (≥4 weeks) (n = 36) vs. statin-naïve ACS (n = 67) and controls (n = 30) in Chinese ACS patients [59].
B. dentium	[40]					
Collinsela	[45]					↓Abundance upon escitalopram treatment compared with baseline in Chinese MDD patients (n = 30) [60].
C. massiliensis		[61]				
C. aerofaciens	[51]					
Dermabacter	[45]					
Propionibacterium	[45]					
Citrobacter	[45]					
Escherichia	[45,62]		↑Abundance upon metformin treatment in healthy young Danish men (n = 27) [63]. ↓Abundance upon empagliflozin treatment in drug-naïve T2DM patients with CDV risks [64]. ↑Abundance in T2DM patients treated with metformin (n = 93) compared with untreated T2DM (n = 106) [65]. ↑Abundance in treatment-naïve T2DM patients treated with metformin (n = 25) [66].		↑Escherichia/Shigella upon duloxetine treatment (30–60 mg/day, 8 weeks) in Chinese IBS patients with depression [67].	
E. coli	[18,40,53,68]	[61]	↑Abundance upon metformin treatment in T2DM patients [65]. ↑Abundance in overweight/obese adults (n = 121) with prior solid tumor treatment after 6–12 months upon metformin treatment [69]. ↓Abundance in T2DM patients with non-alcoholic fatty liver			

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Table 1 (*continued*)

Taxa	GUS	Sulfatase	Antidiabetic drugs	Antihypertensives	Antidepressants	Lipid-lowering drugs
			disease treated with combined metformin and exenatide treatment vs. metformin alone [48].			
Edwardsiella	[45]					
Tannerella	[45]					
Bacteroidota	[70]		↑Abundance upon metformin treatment (0.5 g × 3/day, 12 weeks) in obese T2DM patients (n = 30) [71].			
Bacteroides	[36,45,62,72]		↓Abundance in treatment-naïve T2DM patients (n = 25) upon metformin treatment [73]. ↑Abundance upon dulaglutide treatment, as reported in a systematic review of 38 studies [74].		↑Abundance upon TCAs treatment in population from a Dutch population cohort (n = 1135) [75]. ↑Abundance upon antidepressant treatments in adults from a Dutch population cohort (LifeLines-DEEP, n = 1174), IBD patients (n = 300), and IBS patients with matched controls (n = 341); association lost significance after correction for PPI use [76]. ↓Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (n = 26) [77].	
B. distasonis	[51]		↑Abundance upon metformin treatment in healthy individuals (2 × 850 mg/day, 7 days; n = 35) and in newly diagnosed T2DM patients (n = 50) [78].			
B. vulgatus	[51,53]		↓Abundance upon acarbose treatment in PCOS patients (n = 11) [79].			
B. fragilis	[51,53]	[61]	↓Abundance in newly diagnosed T2D patients (n = 22) upon metformin treatment [80]. ↓Abundance in African American youth with T2DM treated with combined metformin and liraglutide [81].			
B. capillosus	[40]					
B. thetaiotaomicron	[51]	[82]				
B. ovatus	[40,53]		↓ Abundance in African American youth with T2DM treated with combined metformin and liraglutide [81].			
B. uniformis	[51]					
Parabacteroides johnsonii	[40]					
Parabacteroides merdae	[40]					↓Abundance upon prior chronic statin use (≥4 weeks) (n = 36) vs. statin-naïve ACS (n = 67) and controls (n = 30) in Chinese ACS patients [59].
A. obesi		[61]				
Bacillota	[70]		↓Abundance upon gemigliptin–metformin in drug-naïve overweight/obese T2DM patients (n = 70) [83]. ↑Abundance upon metformin treatment in obese PCOS women (n = 29) [84].			↑Abundance upon atorvastatin treatment (20 mg/day) in newly diagnosed hypercholesterolemic East Chinese subjects (n = 202) [50]. ↑Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (n = 26) [77].

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Table 1 (*continued*)

Taxa	GUS	Sulfatase	Antidiabetic drugs	Antihypertensives	Antidepressants	Lipid-lowering drugs
						↑Abundance upon statin treatment combined with metformin or aspirin in T2DM patients (MetaCardis cohort, *n* = 2173); adults with varying cardiometabolic disease severity from Denmark, Germany, and France) [85].
Clostridium	[45,62]		↓Abundance in healthy young Danish men (*n* = 27) following metformin treatment [63]. ↑Abundance upon metformin treatment (0.5 g × 3/day, 12 weeks) in normal-weight T2DM patients (*n* = 30) [71].	↑Abundance in hypertension patients treated with ACEI/ARB (*n* = 36) vs. untreated patients (*n* = 19) [86]	↑Abundance in the genus *Clostridium IV* following venlafaxine treatment (*n* = 2241) [87] ↑Abundance (*Clostridium leptum*) following TCA (amitriptyline, maprotiline, clomipramine) use across three Dutch cohorts (LifeLines-DEEP, 1000IBD, and IBS; total n ≈ 2400 adults) [23].	
C. bartlettii	[40]		↓Abundance in healthy individuals and newly diagnosed T2DM patients (*n* = 50) upon metformin treatment (2 × 850 mg/day for 7 days; *n* = 35) [78]			
C. bifermentans	[53]					
C. butyricum	[53]					
C. clostridioforme	[51]					
C. innocuum	[51]					
C. paraputrificum	[51]					
C. perfringens	[18,51,53]		↑Abundance in obese PCOS women (*n* = 29) treated with combined metformin and exenatide vs. metformin alone [84].			
C. ramosum	[51]					
C. sp. Marseille-P2538	[18]					
Marvinbryantia	[45]					
Bryantella formatexigens	[40]					
Roseburia	[45]		↓Abundance upon acarbose treatment in PCOS patients (*n* = 11) [88]. ↑Abundance in treatment-naïve T2DM patients with CDV risks taking empagliflozin [64]. ↓Abundance in overweight/obese adults with prior solid tumor treatment (*n* = 121) taking metformin for 6–12 months [69]. ↑Abundance upon combined metformin and linagliptin treatment in Mexican adults with prediabetes (*n* = 167) [47].	↑Abundance upon loop diuretics combined with aspirin, ACE inhibitors, or β-blockers in T2DM patients (MetaCardis cohort, *n* = 2173; adults with varying cardiometabolic disease severity from Denmark, Germany, and France) [85].	↑Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (*n* = 26) [77].	
R. hominis	[18,36]					
R. intestinalis	[36]					
R. inulinivorans	[18]					
Lactobacillus	[45,62]		↑Abundance upon α-glucosidase inhibitor treatment in T2DM patients [46,89]. ↓Abundance in treatment-naïve overweight/obese T2DM patients (*n* = 70) following gemigliptin-metformin treatment [83]. ↑Abundance in T2DM patients with non-alcoholic fatty liver disease treated with combined metformin and exenatide		↓Abundance in Chinese MDD patients (*n* = 30) following escitalopram treatment compared with baseline [60].	↑Abundance upon atorvastatin treatment (20 mg/day) in newly diagnosed hypercholesterolemic East Chinese subjects (*n* = 202) [50].

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Table 1 (*continued*)

Taxa	GUS	Sulfatase	Antidiabetic drugs	Antihypertensives	Antidepressants	Lipid-lowering drugs
			treatment vs. metformin alone [48].			
L. brevis	[90]					
L. gasseri	[40,90]					
L. rhamnosus	[18,90]					
L. acidophilus	[53]					
Ruminococcus	[40]		↓Abundance upon α-glucosidase inhibitor treatment in T2DM patients [89]. ↑Abundance following dulaglutide treatment, based on a systematic review of 38 studies [74].		↑Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (n = 26) [77].	↑Abundance in Chinese ACS patients with chronic statin use (≥4 weeks) (n = 36) vs. statin-naïve ACS (n = 67) and controls (n = 30) [59].
R. gnavus	[18,40]					
Faecalibacterium	[45]		↑Abundance upon α-glucosidase inhibitor treatment in T2DM patients [89]. ↑Abundance upon empagliflozin treatment in drug-naïve T2DM patients with CDV risks [64] ↑Abundance upon metformin treatment in drug-naïve T2DM patients (n = 25) [66].		↑Abundance after 8 weeks of vortioxetine hydrobromide (10 mg/day) in MDD Chinese patients (n = 26) [77]. ↑Abundance in Chinese IBS patients with depression following duloxetine treatment (30–60 mg/day, for 8 weeks) [67].	↑Abundance upon atorvastatin treatment (20 mg/day) in newly diagnosed hypercholesterolemic East Chinese subjects (n = 202) [50].
F. prausnitzii	[18,36,40]			↓Abundance upon ACE inhibitor or calcium channel blocker treatment [24].		↑ Abundance in atorvastatin-treated hypercholesterolemic patients (n = 27), compared with untreated hypercholesterolemic patients (n = 15) and healthy subjects (n = 19) [56].
Others species						
Streptococcus agalactiae	[18]					
Peptococcus niger		[91]				
Subdoligranulum variabile	[40]					
Hungatella hathewayi		[61]				
Enterococcus faecalis	[53]		↑Abundance upon α-glucosidase inhibitor treatment in Chinese patients with T2DM [58]. ↓Abundance in T2DM patients with non-alcoholic fatty liver disease treated with combined metformin and exenatide treatment vs. metformin alone [48].			
Eubacterium eligens	[61]				↓Abundance upon TCAs treatment in a Dutch population cohort (n = 1135) [75].	

Bold type indicates bacterial phyla; underlining denotes bacterial genera; italics indicate species names.
Abbreviations: ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; CDV: cardiovascular disease; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; MDD: major depressive disorder; PCOS: polycystic ovary syndrome; PPI: proton pump inhibitor; SSRIs: selective serotonin reuptake inhibitors; T2DM: type 2 diabetes mellitus; TCAs: tricyclic antidepressants.

highlights how their abundance is altered in response to commonly prescribed medications in postmenopausal women, focusing on antidiabetic, antihypertensive, antidepressant, anxiolytic, and lipid-lowering drugs, based on evidence from human studies.

A recent study conducted on women with HIV [92] found that microbial species from the phyla Actinobacteria, Bacteroidota, Euryarchaeota, Bacillota, and Proteobacteria were linked to menopausal status. Among them, species belonging to the Bacillota phylum showed a general decrease in abundance. Interestingly, Bacillota species that were depleted during menopause were positively associated with GUS activity, whereas menopause-enriched species displayed negative associations with GUS, suggesting a functional shift in the GUS potential of the gut microbiome across the menopausal transition. Collectively, clinical studies show that pharmacological modulation of the gut microbiota predominantly affects taxa within the Bacillota, Actinobacteria, Bacteroidota, and Proteobacteria phyla (Table 1). These phyla encompass several genera that harbor GUS activity, including *Faecalibacterium*, *Roseburia*, *Eubacterium*, and *Bifidobacterium*, which are central players in intestinal metabolic and redox homeostasis. In contrast, although Bacteroidota and Proteobacteria also contribute to the GUS pool, their modulation by pharmacological treatments appears less consistent and often context-dependent, varying across drug classes.

Interestingly, the intestinal GUS system is far more represented than sulfatase activity. Whereas GUS genes are widely distributed, sulfatase activity is restricted to a narrow subset of microbes, primarily within the *Bacteroides* and *Bifidobacterium* genera, which express measurable

sulfatase activity. This disparity suggests that GUS-mediated deconjugation represents the dominant microbial route for xenobiotic and estrogen recycling in humans. Across human gut commensals, taxa with concurrent GUS and sulfatase activities include *B. bifidum*, *B. breve*, *Collinsella massiliensis*, *E. coli*, *B. fragilis*, *B. thetaiotaomicron*, and *Alistipes obesi*. By contrast, species carrying only sulfatase genes appear much less represented, with only *Peptococcus niger* and *Hungatella hathewayi* exhibiting sulfatase activity, which remain unexplored in the pharmacological context (Table 1).

Antidiabetic drugs, particularly metformin, are the pharmacological group with the most extensive and consistent evidence of gut microbiome modulation. Beyond its metabolic actions, metformin-driven shifts in GUS-active taxa could alter the functional capacity of the estrobolome, potentially influencing estrogen deconjugation and enterohepatic circulation in postmenopausal women. Across diverse human cohorts, metformin treatment is repeatedly associated with increased abundance of Actinobacteria, particularly *Bifidobacterium* spp., and certain Bacillota such as *Clostridium* and *Lactobacillus*. For instance, *Bifidobacterium bifidum*, *B. longum*, and *B. adolescentis* are more abundant in patients with type 2 diabetes (T2D) treated with metformin [46,55,93]. These increases have also been observed when metformin is combined with α-glucosidase inhibitors or incretin-based therapies (linagliptin, exenatide), suggesting a convergent enrichment of saccharolytic and SCFA-producing genera that help maintain intestinal redox and metabolic homeostasis [84]. Within Proteobacteria, *E. coli* frequently expands after metformin therapy [65,69,94]. Nonetheless, combination treatments with GLP-1 receptor agonists, such as exenatide, have been shown to reduce *E. coli* levels [48], indicating that the gut microbiome response depends on the pharmacological context. The same pattern is observed in *Clostridium* spp., where metformin monotherapy or gemigliptin–metformin combinations differentially modulate abundance depending on patient metabolic status (normal weight vs. obese) [63,71]. Altogether, these data suggest that the gut microbiota mediates metformin efficacy and tolerance, with several GUS-active genera (e.g., *Bacteroides*, *Bifidobacterium*, *Clostridium*) playing central roles in carbohydrate metabolism and intestinal deconjugation reactions.

The second most extensively studied group comprises antidepressant drugs. Antidepressant exposure consistently associates with changes in *Bifidobacterium* [23,77], *Collinsella* [60], *Bacteroides* [75,77,95], *Roseburia* [77], and *Faecalibacterium* [67,77] pointing toward a marked effect on butyrate-producing Bacillota and Actinobacteria. In a Chinese cohort, *Bifidobacterium* spp., *Roseburia*, *Faecalibacterium*, and *Ruminococcus* increased after 8 weeks of vortioxetine treatment in patients with major depressive disorder (MDD), while *Bacteroides* abundance decreased [77]. SNRIs such as duloxetine increased *F. prausnitzii* and the ratio *Escherichia/Shigella* in patients with depression and irritable bowel syndrome [67]. *Collinsella massiliensis*, another Actinobacteria species harboring both enzymatic activities, decreased after escitalopram treatment in patients with major depressive disorder [60]. Given *Collinsella*'s association with pro-inflammatory lipid metabolism, its reduction may contribute to the anti-inflammatory and metabolic improvements observed with antidepressant therapy.

Beyond taxonomic composition, several independent cohorts highlight microbial α- and β-diversity as potential predictors of antidepressant response. Increased α-diversity at baseline or after treatment has been repeatedly associated with remission or clinical response [96]. However, findings are not uniform, as some studies reported higher α-diversity in non-responders [97] or no correlation with baseline microbiota richness [98]. β-Diversity metrics have also been associated with antidepressant class, particularly for SNRIs, which induce distinct community-level shifts [99]. Given that many of the affected genera (e.g., *Bifidobacterium, Roseburia*) belong to the estrobolome, antidepressant-induced changes may extend beyond neurotransmitter pathways, influencing estrogenic homeostasis by modulating GUS-positive communities.

Although reviewing preclinical evidence was not the primary objective, it is worth noting that additional evidence supports a bidirectional interaction between antidepressants and the gut microbiota. In animal models of stress-induced anxiety and depression, the 5-HT_1A receptor agonist buspirone reduced the abundance of Proteobacteria and increased that of *Bacteroides* and *Roseburia*, suggesting restoration of microbial balance in parallel with behavioral improvement [100]. These results, although obtained in mice, provide mechanistic insight into how serotonergic modulation can reshape gut microbial communities.

Among lipid-lowering drugs, statins have received particular attention. Treatment with atorvastatin or long-term statin use in patients with acute coronary syndrome (ACS) leads to significant increases in Actinobacteria (including *Bifidobacterium* and *B. longum*), Bacillota (e.g., *F. prausnitzii*, *Roseburia*), and *Ruminococcus*, alongside decreases in *Bacteroides* and *Parabacteroides* species [50,56,59]. Furthermore, large-scale data from the MetaCardis cohort demonstrated that statins, particularly when combined with metformin or aspirin, enhance gut microbiome richness and increase the abundance of Bacillota and *Roseburia* in T2D patients [85]. Interestingly, several taxa modified by statin therapy, such as *Bifidobacterium*, are GUS-positive and express measurable sulfatase activity (Table 1). This dual enzymatic potential highlights broader intersections among lipid-lowering medications, microbial estrogen metabolism, and cardiometabolic protection in postmenopausal women. The modulation of both GUS- and sulfatase-positive communities thus reinforces the notion that chronic drug exposure can reshape the functional landscape of the estrobolome.

Although much less frequently studied, antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers have been linked to specific microbial patterns. In particular, *F. prausnitzii* abundance decreases under ACEI or calcium channel blocker treatment [24], whereas ACEI/ARB therapies have been associated with increases in *Clostridium* spp. [101]. Since *F. prausnitzii* is a major butyrate producer and anti-inflammatory commensal, these alterations could have implications for intestinal barrier integrity and systemic inflammation, especially in postmenopausal women, where Bacillota depletion has been described. Besides, treatment with sartans has been shown to reduce α-diversity and significantly alter β-diversity, indicating broad alterations in gut microbial community structure without specifying the bacterial taxa involved [75]. However, the limited number of studies of this drug family precludes definitive conclusions.

Overall, the clinical evidence indicates that studies on pharmacological modulation of gut bacteria are dominated by those involving antidiabetic agents. This is followed by antidepressants and anxiolytics, lipid-lowering therapies, and, to a lesser extent, antihypertensive drugs.

Finally, no studies were identified for osteoporosis treatments, another important group of drugs commonly prescribed to postmenopausal women. Although clinical data on the effects of osteoporosis medications on GUS- or sulfatase-active taxa are lacking, emerging preclinical evidence suggests that bone-targeting drugs can modulate the gut microbiota and related metabolic pathways. In particular, alendronate, one of the most prescribed bisphosphonates, has been shown to enhance gut microbial diversity and reshape microbiota composition in ovariectomized rat models of postmenopausal osteoporosis (PMOP) [102]. Similarly, administration of GSD, a gut microbiota-targeted formulation with osteoprotective activity, corrected PMOP-associated metabolic alterations and restored the abundance of butyrate-producing genera such as *Ruminococcus* [103]. These changes collectively support the existence of a gut-bone axis, in which microbial metabolites, bile acid transformations, and SCFA production may contribute to bone homeostasis.

In parallel, there is increasing evidence that the gut microbiota can influence host responses to drugs by enzymatically modifying their chemical structure [72]. This may affect drug bioavailability, efficacy, and toxicity, which is related to an emerging field known as pharmacomicrobiomics [104]. For instance, distinct structural classes of GUS

enzymes, including Loop 1, Mini-Loop 1, and flavin mononucleotide-binding variants, have been shown to efficiently reactivate small-molecule xenobiotics, such as anticancer agents, non-steroidal anti-inflammatory drugs, and other toxicants [105,106]. These reactivations can lead to gastrointestinal toxicity, compromising therapeutic outcomes [107]. In this context, selective inhibitors of bacterial GUS enzymes, including FDA-approved drugs with piperazine and piperidine moieties, have shown promise in mitigating these adverse effects by disrupting gut microbial GUS enzymes through their catalytic-cycle interception [106]. Such inhibition has been associated with altered microbial deconjugation of endobiotics and measurable downstream physiological effects in vivo, underscoring the clinical relevance of drug–GUS interactions [108].

Interestingly, a recent randomized, double-blind, placebo-controlled clinical trial provided compelling evidence of a direct modulation of estrogen homeostasis by specific GUS-active bacterial strains in women transitioning to menopause. The study evaluated a probiotic formulation containing *Levilactobacillus brevis* KABP052 combined with *Lactiplantibacillus plantarum* and *Pediococcus acidilactici*. After 12 weeks of supplementation, peri- and postmenopausal women receiving the probiotic exhibited significantly higher serum concentrations of estradiol (E2) and estrone (E1) than those in the placebo group [90]. These findings demonstrate, for the first time, that targeted modulation of GUS-active taxa can help maintain circulating estrogen levels in this population and counteract the estrogen decline associated with menopause. Although probiotic interventions were excluded from the search criteria, this study was included because of its unique relevance: it represents the only clinical evidence in postmenopausal women demonstrating that modulation of gut GUS-active taxa can directly influence estrogen homeostasis.

Another interesting field of research relates to dietary interventions. To the best of our knowledge, no studies have directly described how dietary compounds modulate GUS or sulfatase-active microbial taxa. However, indirect evidence supports this connection. For instance, an elegant randomized clinical trial conducted in patients with metabolic syndrome evaluated the probiotic effects of pomegranate extract and reported increased abundance of *Lactococcus* in individuals receiving antidiabetic, lipid-lowering, and antihypertensive treatments, as well as increased abundance of *Bifidobacterium* in those treated with antidiabetic and lipid-lowering drugs. Conversely, *Clostridium* levels decreased in non-medicated patients following pomegranate consumption [24].

These findings reinforce that diet and natural supplements can modulate microbial populations linked to the estrobolome. In postmenopausal women, these microbial transformation pathways could contribute to systemic redox balance and estrogen-like signaling, providing a dietary approach to modulate estrogen homeostasis.

5. Knowledge gaps and future directions

Therapeutic modulation of the gut microbiota represents a promising strategy for managing menopausal symptoms and supporting systemic health. However, despite the growing recognition of the gut microbiota's role in hormonal regulation and metabolic homeostasis, significant knowledge gaps remain regarding its interaction with menopausal changes and commonly prescribed medications.

Current evidence suggests that hormonal fluctuations during menopause influence both the composition and functionality of the gut microbiota, yet the directionality, consistency, and clinical consequences of these changes remain incompletely understood.

One major limitation is the lack of longitudinal studies assessing changes in gut microbiota during the menopausal transition. Most available research is cross-sectional, precluding causal inference and mechanistic interpretation. In contrast, no studies have specifically addressed how long-term pharmacological treatments modulate gut microbiota, particularly GUS- and sulfatase-active taxa, in postmenopausal women. This represents a critical point, given the high prevalence of polypharmacy in this population.

Moreover, substantial heterogeneity in study design, population size, sequencing platforms, and bioinformatic pipelines hinders direct comparisons across studies. In addition, there is a marked underrepresentation of diverse ethnic and geographic populations, which limits the generalizability of current findings and may overlook culturally specific patterns of diet, pharmacological interactions, and the gut microbiota.

With this landscape, the estrobolome emerges as a particularly relevant but poorly understood component. Importantly, the contribution of estrobolome-derived estrogens to circulating estrogen levels cannot currently be directly quantified, as reabsorbed estrogens are chemically indistinguishable from endogenous sources. Consequently, estrobolome activity is inferred using complementary approaches, including profiling of free and conjugated estrogens, assessment of fecal β-glucuronidase or sulfatase activity, and gut microbiota taxonomic and functional analyses.

Estrobolome dysfunction has been proposed to contribute to hormonal imbalance, chronic low-grade inflammation, and increased risk of cardiometabolic and hormone-dependent disorders in postmenopausal women. Nevertheless, the functional and clinical characterization of this microbial subsystem, as well as its interactions with dietary polyphenols, fibers, pharmacological treatments, and host genetic factors, remains scarce.

In this regard, future research should prioritize: i) longitudinal cohort studies with greater inclusion of diverse populations to track temporal dynamics of gut microbiota changes during and after menopause and to capture better host-microbiome-drug interactions across varied genetic, dietary and environmental contexts; ii) mechanistic studies elucidating the causal role of the gut microbiota (particularly estrobolome) in estrogen metabolism, systemic inflammation, and mood regulation in postmenopausal women; iii) interventional trials exploring microbiota-targeted strategies, such as polyphenol-rich dietary patterns, increased fiber intake, or omega-3 supplementation, as adjuncts or alternatives to conventional hormone replacement therapy, with particular attention to interindividual variability, and iv) integration of pharmacomicrobiomics, addressing how chronic medication use modulates the estrobolome and how these microbial shifts, in turn, influence drug metabolism, efficacy, and tolerability.

A systems-level understanding of these interactions will be crucial to translate gut microbiome science into personalized interventions that sustain hormonal balance, metabolic resilience, and overall well-being in postmenopausal women.

6. Conclusions

Long-term pharmacological treatments can reshape global gut microbial ecology and alter the functional dynamics of the estrobolome. Given its central role in estrogen deconjugation, xenobiotic metabolism, and redox regulation, elucidating drug-estrobolome interactions may be essential for optimizing pharmacotherapy aimed at improving postmenopausal health outcomes, particularly in the context of hormone replacement strategies.

The current lack of clinical studies specifically addressing how long-term medication use affects GUS- and sulfatase-active taxa in postmenopausal women highlights a major research gap. Integrating pharmacomicrobiomics with menopausal research could provide new insights into how medication, diet, and microbiota jointly influence estrogen and metabolic homeostasis.

Contributors

María Elena Martínez-Nortes contributed to methodology, data curation, investigation, formal analysis, writing, original draft preparation, review and editing.

Concepción Carrascosa-Romero reviewed and edited the manuscript.

María Ángeles Ávila-Gálvez contributed to conceptualization,

methodology, data curation, investigation, formal analysis, writing, review and editing.

Juan Carlos Espín contributed to conceptualization, methodology, writing, review and editing, and was responsible for project funding and supervision.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Ethical approval

This manuscript is a narrative review and does not involve new studies with human participants, animals, or identifiable personal data. For this reason, ethical approval and informed consent were not required.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly Premium (Grammarly Inc., California, USA) to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This work was supported by project PID2022-136419OB-100 (Ministerio de Ciencia, Innovación y Universidades, MICIU, AEI/10.13039/501100011033, Spain), co-funded by the European Union through the "ERDF A way of making Europe" programme; by the AGROALNEXT programme (PRTR-C17.I1, MICIU, Spain), co-funded by the NextGenerationEU; and by Fundación Séneca (Comunidad Autónoma de la Región de Murcia, Spain).

Declaration of competing interest

The authors declare that they have no competing interest.

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