



Review Article

Targeting Gut Microbiota-derived β -glucuronidase to Reduce Enterotoxicity: Research Progress on Strategies and Prospects for the Application of Food and Medicine Homology

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Abstract: The gut microbiome-encoded β -glucuronidases (GUS) play a significant role in human health by metabolizing both endogenous and exogenous substances in the gastrointestinal (GI) tract. These enzymes catalyze the hydrolysis of β -D-glucuronides, reversing glucuronidation reactions carried out by the liver. While this process is essential for certain metabolic functions, it can also lead to harmful consequences, including drug toxicity and intestinal damage. In recent years, the inhibition of bacterial β -glucuronidases (BGUSs) has emerged as a promising strategy for mitigating drug-induced toxicity and improving therapeutic outcomes. However, the genetic diversity, functional complexity, and variable inhibitor responses of GUS enzymes present significant challenges in developing effective inhibitors tailored to specific pharmacological and pathological contexts. This review provides an in-depth examination of GUS enzyme function, structural characteristics, and sources, followed by a discussion of GUS-mediated intestinal toxicity arising from both endogenous and exogenous compounds. We also highlight recent advances in the development and application of GUS inhibitors, with particular emphasis on natural compounds derived from food and medicinal sources. Finally, we explore the prospects and challenges associated with GUS-targeting strategies, underscoring their potential for therapeutic applications.

Keywords: β -glucuronidase; enteric toxicity; targeted strategy; food and medicine homology

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1 Introduction

The human gut microbiota is a complex and ever-evolving community of microorganisms that plays a vital role in maintaining overall health and well-being. It serves as the central hub of the host-microbe symbiotic relationship, marked by exceptional diversity and a relatively stable equilibrium. The core constituents of the gut flora predominantly encompass members of the phylum *Bacteroidetes* and the phylum *Firmicutes*, which play a pivotal role in upholding intestinal homeostasis. These key microbial communities have a wide-ranging impact on both gut health and overall bodily function by regulating metabolism, maintaining intestinal barrier integrity, controlling inflammatory responses, and supporting processes like hematopoiesis, among other critical physiological roles^[1,2]. A substantial cohort of enzymes expressed by the intestinal flora are involved in metabolic

processes by catalyzing reactions such as the hydrolysis and reduction of exogenous as well as endogenous compounds. In concert with the binding and oxidative reactions mediated by the host's metabolic system, these proteins regulate the balance of internal compounds and facilitate the elimination of external substances^[3]. Among these enzymes, β -glucuronidase (GUS) has emerged as a prominent focus of research. β -Glucuronidase is expressed in humans (human GUS, HGUS) and a variety of gut bacteria (gut bacterial GUS, BGUS), and it exerts a significant regulatory effect on metabolite levels by catalyzing the hydrolysis of glucuronic acid conjugates, thereby liberating free drugs or endogenous metabolites^[4]. While GUS enzymes are essential for processes like drug reactivation, hormone metabolism, and the cycling of endogenous metabolites, their activity can also lead to intestinal toxicity and is a major contributing factor to drug-induced adverse effects^[5]. The catalytic reactivation of metabolites

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by GUS enzymes can provoke localized inflammation within the intestinal tract. The release of drugs and endogenous toxic metabolites, particularly in individuals with a pre-existing compromised immune system, can culminate in damage to the intestinal epithelium, the disruption of the intestinal barrier, and can contribute to the development of conditions like inflammatory bowel disease (IBD). Given that a vast array of commercially available drugs undergo metabolism via glucuronidation, GUS-mediated deglucuronidation has been implicated in colon carcinogenesis and genotoxicity, as well as the dose-limiting toxicity of anticancer drugs and non-steroidal anti-inflammatory drugs (NSAIDs), side effects that restrict their therapeutic effectiveness and clinical use. In addition, the activity of GUS enzymes influences intestinal health through the regulation of intestinal microbiota composition. For instance, the hydrolysis of drugs or metabolites by specific GUS enzymes may promote the proliferation of certain pathogenic bacteria, perturbing the equilibrium of the intestinal microbiota and culminating in dysbiosis and intestinal pathological alterations^[6].

In recent years, substantial progress has been made in investigating GUS enzyme-mediated intestinal toxicity^[7], highlighting its critical role in the development of toxicity linked to exogenous compounds such as the anticancer drug irinotecan and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as endogenous metabolites like bilirubin, hormones, and neurotransmitters^[8-12]. GUS enzyme-mediated drug metabolism within the intestinal microbiota is responsible for causing delayed diarrhea in patients with advanced colorectal cancer who are undergoing irinotecan treatment^[13], and for the onset of enteropathy resulting from prolonged utilization of NSAIDs (e.g., diclofenac, ketoprofen, indomethacin, *et al.*)^[14]. Additionally, the detoxification of certain foodborne carcinogens, such as heterocyclic aromatic amines (HAAs), by host UDP-glucuronosyltransferases (UGTs) can be reversed by intestinal bacterial GUS enzymes, increasing cancer risk, particularly for colon cancer^[15]. Furthermore, individual variations in GUS enzyme activity are thought to significantly influence differences in drug efficacy and toxicity. While existing studies have begun to uncover the mechanistic underpinnings of GUS enzymes in intestinal toxicity, aspects such as their substrate specificity, activity modulation, and the intricate relationship with the composition of the intestinal flora remain incompletely elucidated^[16]. Concurrently, the specificity and efficacy of intervention strategies directed at GUS enzymes urgently necessitate further corroboration. Current approaches to inhibiting GUS enzymes include the use of antibiotics, synthetic inhibitors, and natural inhibitors. However, each of these intervention strategies harbours drawbacks: for instance, antibiotic administration can precipitate dysbiosis, while the safety profile of synthetic inhibitors demands verification. In contrast, natural inhibitors have emerged as a promising area of research due to their potential efficacy and lower risk of side effects. Nevertheless, given the vast diversity of natural compounds derived from various sources, current research remains limited, and more extensive exploration and development are needed to fully realize their potential across different applications (Fig. 1).

This comprehensive review is designed to systematically compile and summarize the origin, structural characteristics, and functional modalities of GUS enzymes. It will delve into the principal mechanistic pathways through which these enzymes orchestrate intestinal toxicity, examine the critical factors that exert an influence on the activity of GUS enzymes, and highlight

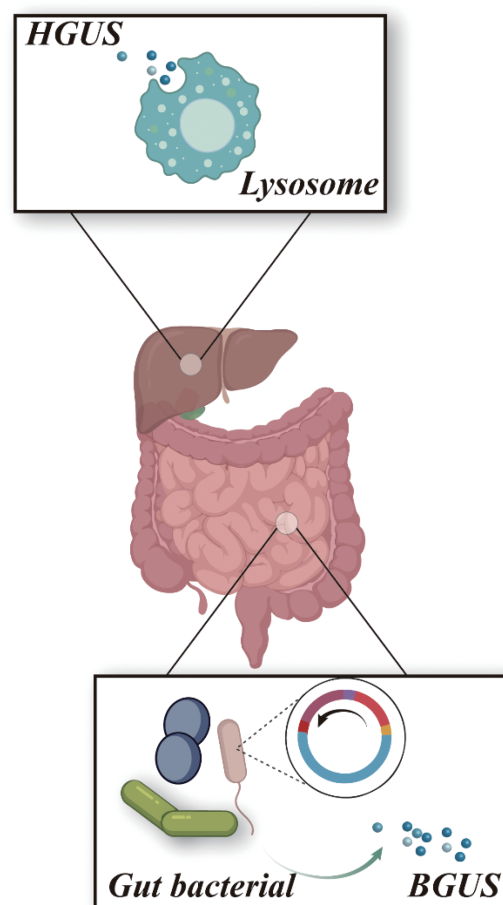


Figure 1 Sources of GUS enzymes in the human body.

targeted intervention strategies, with a focus on their potential applications in drug therapy. The ultimate goal is to provide a solid theoretical foundation and practical insights that can drive further research and support the clinical translation of findings in this emerging field.

2 Provenance, architecture and function of GUS enzymes

2.1 Origins of GUS enzymes

GUS enzymes originate from a variety of sources, including animals, plants, and bacteria. In plants, GUS enzyme activity has been extensively studied across multiple species, with notable examples including *Arabidopsis thaliana*, rice, tobacco, and maize. In these plants, GUS appears to be closely linked to growth and development, as its activity tends to be higher in younger, actively growing tissues compared to mature or fully developed plant structures^[17]. Additionally, the β -glucuronidase (GUS) gene serves as a valuable tool for studying gene expression patterns and spatial localization. The GUS reporter gene system is widely used in plant biotechnology due to its ease of use, rapid detection, high sensitivity, and cost-effectiveness, while also eliminating the need for radioisotopes. These advantages have made it a standard technique for assessing gene activity in various plant research applications^[18]. GUS is also discernible in organisms categorized under invertebrate taxa, such as oysters^[19], snails^[20], and

nematodes^[21]. GUS activity has likewise been detected in *Drosophila*^[22] and assorted species of locusts^[20]. In recent years, research on GUS enzymes has increasingly focused on their role in the human body, which has two primary sources: human GUS (HGUS), produced endogenously, and bacterial GUS (BGUS), synthesized by gut microbiota (Fig. 1). Human β -glucuronidase represents an acid hydrolase that manifests expression across a panoply of tissues and body fluids. Substantial inter-individual heterogeneity exists in both its activity and expression magnitudes within the liver, kidney, and serum. Roughly one-third of hepatic β -glucuronidase is situated within the lumen of the endoplasmic reticulum (ER)^[23] and is hypothesized to partake in hepatic circulation. β -glucuronidase is also present within the lysosomal compartment of the cell^[23] and plays a role in the hydrolysis of steroid hormone glucuronides^[24]. Human β -glucuronidase occupies a pivotal position in tumorigenesis, metastasis, and disease progression, thereby endowing it with the potential to serve as a promising cancer biomarker^[25].

GUS enzymes are also extensively dispersed throughout the human intestinal microbiota, with particular prevalence in bacterial phyla like *Firmicutes*^[26], *Bacteroidetes*^[27], *Actinobacteria*^[28], *Acidobacteria*^[29], and *Proteobacteria*^[30]. These bacteria modulate the metabolism of drugs and endogenous metabolites by catalyzing the hydrolysis of glucuronide conjugates. GUS enzymes from different bacterial species exhibit variations in substrate specificity and catalytic efficiency. As a result, the composition of the gut microbiota plays a direct role in influencing drug metabolism and the host's response to toxicity. To date, approximately 300 bacterial GUS (BGUS) proteins have been identified^[31].

2.2 Architectural characteristics of GUS enzymes

GUS enzymes belong to Glycoside Hydrolase family 2 (GH2), and their catalytic modality hinges upon two catalytic glutamate residues, namely E413 and E504, situated within the active site. The three-dimensional conformation of GUS enzymes exhibits a high degree of conservation; nevertheless, structural differences among bacterial strains lead to significant variations in substrate specificity and catalytic efficiency^[31]. These enzymes exhibit complex and diverse structural characteristics, varying in amino acid sequence length and deglucuronidation activity. Notably, the BGUS activities of diverse strains belonging to the same species can deviate substantially. For instance, *Faecalibacterium prausnitzii* A2-165 exhibited a PNPG hydrolysis activity of 0.505 U/mg protein, which was more than 20 times higher than that of *Faecalibacterium prausnitzii* L2-6, with an activity of 0.02 U/mg protein^[32]. Even the BGUSs expressed by a single strain may diverge in structure and function. For instance, in the human gut commensal bacterium *Bacteroides hominis*, researchers have identified three distinct GUS proteins. They share analogous TIM barrel core fold characteristics, yet these proteins exhibit different lamellar structures, distinct tertiary and quaternary architectures, and unique structural variations within their active sites^[33]. The distinct structural features of these enzymes contribute to their diverse substrate processing abilities and varied susceptibilities to inhibition, highlighting the extensive range of GUS enzymes.

Multiple sequence alignments of GUS reveal a high level of congruence among active site residues, including catalytic glutamate, N-K motifs, tyrosine, and so forth, as well as the core-predicted α/β hydrolase folds. However, the regions proximal to the active site exhibit pronounced variability in both length and

amino acid composition. The active site of GUS enzymes is typically encircled by multiple loop structures, such as Loop 1 and Loop 2. These loops not only facilitate substrate binding but also play a crucial role in regulating the catalytic efficiency of the enzymes. For instance, the length, conformation, and hydrophobicity of Loop 1 and Loop 2 directly govern the substrate selectivity of the enzyme. Different isoforms of GUS enzymes (e.g., L1-type, L2-type, and acyclic) vary in these loop structures, which consequently impacts their hydrolysis of drug metabolites and endogenous metabolites. Based on the disparities in the loop structures, GUS enzymes can be categorized into multiple diverse isoforms. Researchers have classified BGUSs into seven subtypes, namely Loop 1 (L1), mini-Loop 1 (mL1), Loop 2 (L2), mini-Loop 2 (mL2), mini-Loop 1,2 (mL1,2), No Loop (NL), and No coverage (NC, proteins lacking sequence information for one or both loop regions). L1 and L2 are loops adjacent to the active site that display significant variability in length and amino acid composition. L1 consists of more than 15 residues and is known as the "bacterial loop" in *E. coli* GUS. Specifically, the 356-380 region of *E. coli* GUS encompasses a >15-residue loop. β -glucuronidase of the L1 type accounts for approximately 5.5% of the identified GUS protein sequences. mL1 enzymes possess a 10-15-residue loop at the same position as L1. *Bacillus fragilis* GUS of the phylum Anabaena, featuring a 12-residue loop, represents the mL1 GUS of known structure. mL1 enzymes are relatively abundant, making up approximately 15%–21% of the identified GUS enzymes. They may also contain additional C-terminal carbohydrate-binding domains, which include smaller loops ranging from 10 to 15 residues. L2 is regionally adjacent to L1, located at a distance of three residues from the catalytic glutamate in the amino acid sequence and is variable in length. Like L1, L2 is ≥ 12 residues in length, as seen in BuGUS2 from *Bacillus*, and accounts for 10%–14% of identified GUS proteins. In contrast, mL2 is a shorter loop, ranging from 9 to 11 residues, as found in PmGUS from *Parabacteroides*, and makes up 4%–7% of the total GUS enzymes. mL1,2 accounts for only 1%–2% of the total: its structure combines both mL1 and mL2. The mL1,2 enzyme exhibits a structure with 10–15 residues in the L1 region and 9–12 residues in the L2 region. A representative GUS model from *Bacteroides ovatus* demonstrated that the two closely spaced loops collide at either position, which might elucidate the absence of enzymes containing intact L1 and L2. The NL enzyme, which lacks both loop regions, was the most prevalent GUS (57%) and was present in all samples from the 139 individuals studied^[31]. Recently, 15 NL BGUSs (Fp2GUS from *Faecalibacterium prausnitzii* L2-6, Rh2GUS from *R. hominis*, and Rg3GUS from *Ruminococcus gnavus*, among others) have exhibited FMN-binding ability and are produced by bacteria from the *Clostridia* phylum^[34]. The L1-type and the L2-type GUS enzymes possess a more compact active site structure, rendering them suitable for processing smaller substrates. In contrast, acyclic (NL-type) GUS enzymes feature a more open active site and are capable of handling larger molecules or specialized substrates. Most GUS enzymes assume tetrameric or dimeric configurations, wherein each subunit comprises approximately 500 to 1100 amino acids. Different isoforms of GUS enzymes may possess distinct molecular weights and conformations, further modulating their catalytic properties and substrate affinity^[35]. In summary, human gastrointestinal microbial GUS enzymes possess diverse active sites near their loop structures, which modify a conserved fold. This structural adaptability allows them to process a wide range of chemically diverse substrates present in the gut.

2.3 Operational mechanisms of GUS enzymes

The primary function of GUS enzymes is to catalyze the hydrolysis of glucuronide conjugates. Glucuronidation, a process in which glucuronide molecules are covalently attached to various endogenous and exogenous compounds, plays a crucial role in facilitating the excretion and clearance of these substances from the body through bile and urine (Fig. 2). Intestinal β -glucuronidases (BGUSs) possess the capacity to reverse this inactivation cascade, permitting the reconstitution of the original compounds or their active metabolites within the gastrointestinal (GI) tract. This, in turn, augments their systemic absorption potential or may precipitate direct intestinal damage as a consequence of toxic metabolite generation. For instance, in the case of irinotecan, its metabolite, the SN-38 glucuronide conjugate, undergoes reactivation within the intestinal lumen by the catalytic action of GUS enzymes, giving rise to the more cytotoxic SN-38. This process leads to dose-limiting diarrhea and intestinal mucosal damage, restricting the therapeutic use of the drug^[36]. Moreover, metabolites of NSAIDs, such as diclofenac, ketoprofen, and indomethacin, also experience reactivation in the intestinal milieu by GUS enzyme activity, thereby intensifying the toxic effects of these drugs and exacerbating their adverse profiles^[37]. Beyond drug metabolism, GUS enzymes partake in the circulation and homeostatic regulation of endogenous metabolites (including hormones, bilirubin, neurotransmitters, etc.). The host's uridine diphosphate glucuronosyltransferases (UGTs) and β -glucuronidase system play a crucial role in modulating the metabolism and maintaining the homeostasis of numerous key endogenous substances. The 'estrogenome' pertains to a cluster of genes implicated in estrogen metabolism and encoded by the intestinal flora, among which GUS enzymes are a constituent. These enzymes cleave conjugated estrogens in the gut lumen, releasing free estrogens that re-enter enterohepatic circulation, ultimately leading to an increase in hormone levels^[38]. Reactivation of neurotransmitters by GUS enzymes can also perturb homeostasis. Serotonin (5-hydroxytryptamine [5-HT]) and dopamine (3,4-dihydroxyphenylethylamine [DA]), for example, are neurotransmitters predominantly sequestered in the gastrointestinal tract^[39]. These neurotransmitters establish a

bidirectional communication pathway, known as the gut-brain axis, between the intestinal tract and the central nervous system. Neurotransmitters and their metabolites produced by the gut microbiota are absorbed from the gastrointestinal tract and enter the systemic circulation^[40]. Aberrations in this network have been associated with a spectrum of disorders, ranging from Alzheimer's disease (AD) and Parkinson's disease (PD) to depression and anxiety^[41]. In patients with gallstones, an increased abundance of bacterial species capable of producing GUS enzymes, such as *Escherichia coli*, *Klebsiella*, *Enterococcus faecalis*, and *Mycobacterium anisopliae*, has been observed with an increase in GUS activity in the bile. This enzymatic activity facilitates the release of free bilirubin from its glucuronide conjugates, which then combines with calcium to precipitate as calcium bilirubin, a major constituent of gallstones^[42]. Additionally, the detoxification of certain foodborne carcinogens, exemplified by HAAs, by host UGTs can be disrupted by intestinal BGUSs, leading to the reactivation of carcinogens and an increased risk of colorectal cancer. In the gut, heterocyclic amine glucuronide couplers (HCA-G) can be hydrolysed by bacterial β -glucuronidases, leading to the release of potentially biologically active glycosidic ligands^[43]; the release of N-hydroxylated products may induce mutagenicity through interactions with colonic epithelial cells. Furthermore, in the context of HCA-G, HCA may be reabsorbed into the liver, where it may be activated and potentially damage DNA, or it may be converted back into HCA-G and re-enter the intestine, contributing to the enterohepatic cycle and thus prolonging the duration of HCA exposure^[44].

3 GUS enzymes and intestinal toxicity

The intestinal bacterial GUS enzymes play a key role in hepatic-intestinal recycling and are the primary contributors to GUS enzyme-mediated enterotoxicity. These enzymes are responsible for the reactivation of a wide range of substances, leading to intestinal toxicity and adverse drug effects^[45].

3.1 Drug toxicity mediated by GUS enzymes

Glucuronic acid assumes a pivotal role within the

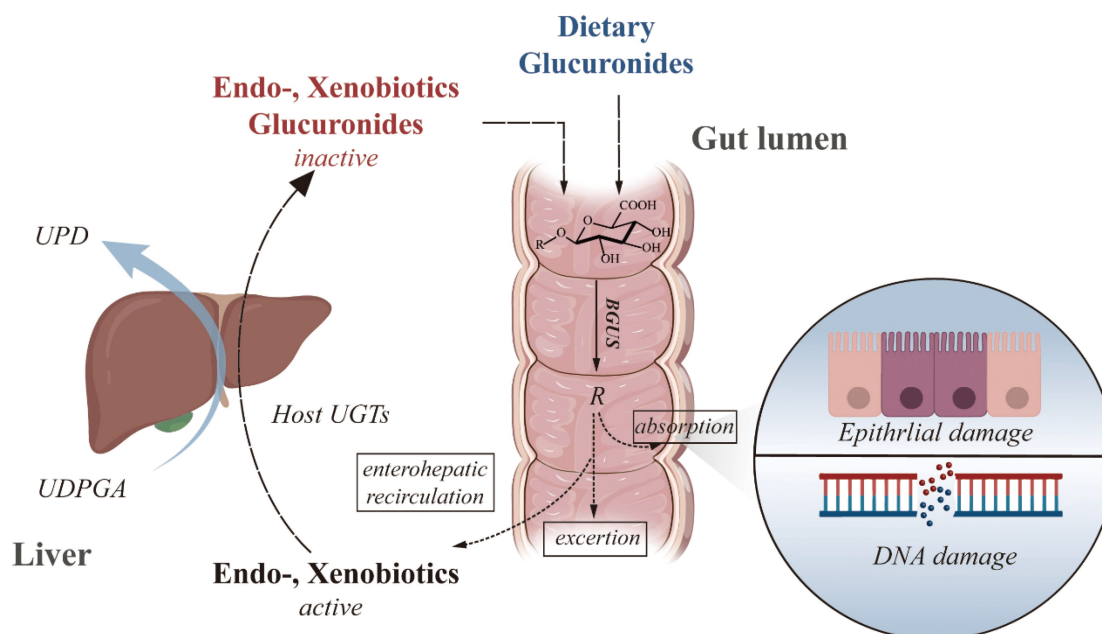


Figure 2 Proposed Mechanism of GUS Enzyme Activity and Its Biological Implications.

biotransformation pathway of drug metabolism. It forms covalent bonds with drugs and endogenous substances that are slated for elimination from the organism, principally occurring within the liver, and is thereafter secreted into the intestine^[46]. The formation of glucuronic acid conjugates typically leads to a reduction in the bioactivity of most compounds. However, β -glucuronidase in the intestinal microbiota can cleave the glucuronic acid moiety, utilizing it as a carbon source and reactivating glycosides that would otherwise be excreted. This enzymatic process leads to the accumulation of reactivated glycosides, which can exert significant toxicity on intestinal tissues. Evidence suggests that these reactivated compounds can trigger severe adverse reactions in humans^[47] (Table 1). The intestinal toxicity of specific drugs is intensified by the production of more noxious metabolites from their glucuronic acid conjugates subsequent to hydrolysis catalyzed by GUS enzymes. Exemplary cases include Irinotecan, a front-line chemotherapeutic agent deployed in the treatment of colon cancer^[48], and Regorafenib, utilized for the management of metastatic colorectal, hepatocellular carcinoma, and gastrointestinal mesenchymal stromal tumors^[8], in addition to the ubiquitously employed NSAIDs^[49] and other relevant pharmacotherapeutics.

3.1.1 Anti-cancer drugs

Irinotecan (CPT-11) is a key chemotherapeutic agent used in the treatment of colorectal and pancreatic cancers, often administered in combination with 5-fluorouracil or oxaliplatin to enhance therapeutic efficacy. Current research is actively investigating its potential use in a wider range of cancer types, aiming to expand its therapeutic applications. Nevertheless, irinotecan is associated with adverse effects such as bone marrow suppression and gastrointestinal (GI) complications, including mucositis and severe diarrheal episodes, which impose dose limitations and curtail its utilization in a wider range of diseases. Diarrhea occurs in approximately 88% of patients undergoing irinotecan treatment, with 30% experiencing severe grade 3-4 diarrhea^[64,65]. These side effects often exhibit a poor response to antidiarrheal pharmacotherapy. Hence, ameliorating the diarrhea induced by irinotecan holds significant clinical importance. The precursor drug of irinotecan undergoes in vivo conversion to SN38, a potent topoisomerase I inhibitor that decelerates the rapid

proliferation of both tumor cells and intestinal epithelial cells, which possess a renewal cycle of every 5 days^[66]. SN38 is detoxified through conjugation with glucuronic acid to yield SN38-G, a metabolite that can be excreted via the digestive tract. However, β -glucuronidase synthesized by intestinal bacteria has the capacity to cleave glucuronic acid from SN38-G, thereby reactivating SN38. This reactivation subsequently leads to epithelial cell damage, resulting in hemorrhagic diarrhea and significant weight loss in animal models^[36].

Regorafenib is an orally administered small molecule kinase inhibitor, whose anti-tumor efficacy relies on the inhibition of the tyrosine kinases VEGF and TIE2. This drug has been extensively employed in the treatment of patients with metastatic colorectal cancer, hepatocellular carcinoma, and gastrointestinal mesenchymal tumors^[67]. Nonetheless, regorafenib is accompanied by certain adverse reactions, with diarrhea being the most prevalent complication^[68]. In the liver, regorafenib is metabolized by UGT enzymes, converted into a glucuronidated form, and subsequently enters the gastrointestinal tract. Here, β -glucuronidase produced by gut microbes can reactivate regorafenib in the gastrointestinal tract, leading to toxic side effects^[69]. Recent research advancements have revealed that the clinical efficacy of regorafenib can be effectively enhanced by inhibiting β -glucuronidase in intestinal microorganisms^[8].

3.1.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs, being among the most prevalently utilized pharmaceuticals globally, are widely employed in the management of osteoarthritis, rheumatoid arthritis, febrile conditions, and a diverse array of pain-related disorders, owing to their potent anti-inflammatory, analgesic, and antipyretic attributes^[70]. Beyond their well-established analgesic, anti-inflammatory, and antipyretic efficacies, NSAIDs have further been demonstrated to confer prophylactic benefits against a variety of life-threatening illnesses, inclusive of cancer and myocardial infarctions. NSAIDs exert their therapeutic actions by inhibiting cyclooxygenase activity and curtailing prostaglandin synthesis^[71]. Nevertheless, data gleaned from multiple placebo-controlled trials and meta-analytic studies indicate that NSAIDs are associated with a spectrum of adverse effects impacting the gastrointestinal, cardiovascular, hepatic, renal, cerebral, and pulmonary systems^[72]. It is widely

Table 1 Metabolism of Endogenous and Exogenous Substances Mediated by GUS Enzyme

Compound	Symptom	Related bacteria	References
Irinotecan	Mucositis and late-onset diarrhea	<i>E. coli</i> , <i>C. perfringens</i> , <i>F. prausnitzii</i> , <i>B. fragilis</i> , <i>B. uniformis</i> , <i>B. ovatus</i> , <i>B. dorei</i> , <i>B. dentium</i>	[47-51]
Regorafenib	Diarrhea	<i>R. gnavus</i> , <i>R. hominis</i> , <i>F. prausnitzii</i>	[8]
Diclofenac	Inflammation, mucosal erosion, increased mucosal permeability, ulceration	<i>R. gnavus</i> , <i>C. perfringens</i> , <i>B. fragilis</i> , <i>E. coli</i> , <i>B. dentium</i> , <i>E. eligens</i> , <i>S. agalactiae</i> , <i>L. rhamnosus</i> , <i>B. ovatus</i> , <i>B. dorei</i> , <i>B. uniformis</i> , <i>P. merdae</i>	[52]
Indomethacin	Gastroduodenal injury, mucosal erosions, ulceration	<i>E. faecalis</i> , <i>Bacteroides</i> , <i>Enterobacteriaceae</i> , <i>C. difficile</i>	[53, 54]
Morphine	Reactivation	<i>E. coli</i> , <i>C. perfringens</i> , <i>B. dentium</i>	[55]
Mycophenolate mofetil	Diarrhea	<i>Firmicutes</i> , <i>Bacteroidetes</i> , <i>Proteobacteria</i>	[56]
Bilirubin	Reactivation	<i>C. perfringens</i> , <i>C. ramosum</i> , <i>C. difficile</i> , <i>B. fragilis</i>	[57, 58]
Estrogen	Reactivation	<i>R. gnavus</i> , <i>F. prausnitzii</i> , <i>S. agalactiae</i> , <i>C. perfringens</i>	[59]
Norepinephrine	Reactivation	<i>Clostridium species</i>	[11]
Dopamine	Reactivation	<i>Clostridium species</i>	[11]
Serotonin	Reactivation	<i>C. ramosum</i> , <i>E. coli</i>	[60]
IQ	Carcinogenesis	<i>E. coli</i>	[61]
PhIP	Carcinogenesis	<i>F. prausnitzii</i> , <i>E. coli</i> , <i>S. typhimurium</i>	[62]
Triclosan	Increased the severity of colitis	<i>F. prausnitzii</i>	[63]

acknowledged that NSAIDs precipitate a variety of adverse reactions within the gastrointestinal tract^[14]. These untoward reactions are reported to manifest in approximately 10% to 60% of patients: dyspepsia and heartburn being observed in 60% of cases, gastric or duodenal ulcers in 20% to 30%, and severe gastrointestinal complications such as perforation and hemorrhage in 1% to 1.5% of patients^[73]. Historically, research has primarily focused on the adverse effects of NSAIDs on the upper gastrointestinal tract, particularly their role in gastric ulceration and mucosal injury. However, with the advent and advancement of video capsule endoscopy and double-balloon endoscopy, more recent attention has been redirected towards the clinical significance of small bowel lesions, including blood loss, ulceration, and perforation^[74]. Small bowel injury is increasingly recognized as a critical complication of NSAID therapy. NSAIDs induce a range of small bowel pathologies, spanning from augmented intestinal permeability, intestinal inflammation, protein loss, blood loss, and ulceration, to perforation and diaphragmatic-like stenosis. Research investigations have ascertained that 30% of severe gastrointestinal events occur in the distal duodenum, and there have even been reported fatalities due to small bowel perforation^[75]. A post-trial analysis of a large clinical outcome trial disclosed that lower gastrointestinal events accounted for 40% of all serious gastrointestinal events in patients treated with NSAIDs^[76]. The high prevalence of NSAID-enteropathy was corroborated by endoscopic evaluations in patients undergoing NSAID treatment, suggesting that approximately 70% of regular NSAID users suffer from small bowel erosions and ulcers^[77].

In contrast to upper gastrointestinal injuries, NSAID-induced small bowel injury (NSI) exhibits complex etiological underpinnings. Multiple factors contribute to NSAID-induced enteropathy (NSI), including the depletion of prostaglandin (PG) E₂, which reduces intestinal mucus production, along with increased intestinal motility and elevated levels of inflammatory cytokines, exacerbating mucosal damage^[78]. Although inhibition of COX-1 and/or COX-2 may contribute to the observed toxicity, certain local effects also play a role. These local effects are mediated by the glucuronide moieties of NSAIDs (and/or their oxidized metabolites). For instance, NSAIDs like diclofenac are detoxified through the conjugation with glucuronic acid by hepatic-resident UGT and subsequently excreted via the bile. In the gut lumen, glucuronic acid is enzymatically cleaved from the drug conjugate by microbial β -glucuronidase. These reactivated substances then inflict damage on the intestinal epithelium, culminating in enteropathy and mucosal injury^[54].

3.1.3 Other drugs

Morphine undergoes metabolic transformation, yielding morphine-3-glucuronide (M3G, accounting for 57.3% and being biologically inactive) and morphine-6-glucuronide (M6G, constituting 10.4% and exhibiting biological activity). These metabolites are excreted into the intestine via the action of host UGT. Subsequently, within the intestinal milieu, both glucuronides are subjected to hydrolysis by GUS enzymes^[55], and are then reabsorbed in the form of morphine. Prolonged morphine use following this process further leads to reduced intestinal secretion and suppressed propulsive colonic motility, contributing to opioid-induced constipation^[79].

Mycophenolate mofetil (MMF) finds its application in the prophylaxis of allograft rejection in renal transplant recipients and is progressively being incorporated into the therapeutic regimens

for all modalities of organ transplantation. Upon oral administration, the metabolically inactive mycophenolate mofetil (MMF) is rapidly absorbed and extensively converted into its active metabolite, mycophenolic acid (MPA), by abundant intestinal esterases. Due to its potent ability to inhibit lymphocyte proliferation, MPA has been recognized as a safe and effective option for preventing allograft rejection^[80]. However, its therapeutic effectiveness is compromised by the occurrence of gastrointestinal (GI) toxicity, which can manifest as mild to severe diarrheal episodes and other associated symptoms^[81]. The underlying cause of GI toxicity has been attributed to multiple mechanisms, among which the enterohepatic recirculation mediated by intestinal bacterial β -glucuronidase is the most prominent. MPA can be metabolized by hepatic UGT to engender glucuronidated MPA (MPAG) and, to a lesser extent, acyl MPAG (AcMPAG)^[82]. Intestinal bacterial GUS enzymes dissociate MPAG back into MPA, which then engages in enterohepatic recirculation, thereby leading to augmented MPA exposure^[83]. Research investigations have substantiated the capacity to both forestall and reverse MMF-induced GI toxicity by curtailing GUS expression and activity, as well as by inhibiting the growth of GUS-producing bacteria. This approach effectively mitigates the catabolism of the MMF metabolite, MPAG, back to free MPA^[84].

3.2 GUS enzyme-mediated endogenous metabolite toxicity

GUS enzymes are not only essential for drug biotransformation but also play a significant role in metabolizing endogenous compounds and regulating their systemic circulation. By cleaving the glucuronic acid moiety, these enzymes can enhance the toxicity of various endogenous substances, particularly affecting bilirubin and hormone metabolism.

3.2.1 Bilirubin

Hyperbilirubinaemia, which occurs in approximately 60% of full-term newborns and 80% of preterm infants on a global scale, is typified by an elevation in the level of physiological unconjugated bilirubin within the serum. Notably, abnormally elevated concentrations of bilirubin possess potential neurotoxic properties^[85]. Unconjugated bilirubin (UCB) represents a yellow, non-polar pigment that is transported to the liver via albumin and subsequently converted into bilirubin-glucuronide by UGT within the endoplasmic reticulum^[86,87]. The conjugated bilirubin is then released into the intestinal lumen for elimination, facilitated by multidrug resistance protein (MRP2), and may be transported back into the bloodstream via MRP3^[88,89]. Following its secretion, the water-soluble conjugated bilirubin undergoes hydrolysis to UCB by the abundant β -glucuronidase present in the brush border of the neonatal intestine, and the unconjugated bilirubin is reabsorbed through passive diffusion. In neonates, elevated levels of bilirubin can disrupt the tight junctions of the intestinal epithelium, leading to an augmentation in the hepatic-intestinal circulation. Moreover, unconjugated bilirubin can cross the blood-brain barrier and infiltrate the central nervous system, potentially causing neurological damage, particularly in conditions such as acidosis, prematurity, infection, hypoxia, and ischemia^[90].

It has been demonstrated that in the hepatobiliary system of rats and the gallbladder bile of 50 Caucasians, there is a pronounced manifestation of endogenous β -glucuronidase activity^[91]. Under specific circumstances, when activated, β -glucuronidase has the capacity to dissociate bilirubin

diglucuronide within the bile, instigating the formation of pigmented gallstones^[92]. In the presence of primary or secondary bacterial infections in the biliary tract, this dissociation process can accelerate, leading to the formation of calcium bilirubinate, a key component of pigment gallstones. Conversely, in the absence of bacterial infections, the process proceeds at a slower pace^[93]. Patients afflicted with gallstones exhibit an increased prevalence of GUS-producing bacteria, concurrent with elevated GUS activity in the bile^[42]. This enzymatic activity facilitates the release of free bilirubin from its glucosinolate conjugates, which then further combines with calcium to precipitate as the principal constituent of brown pigmented stones, namely bilirubin calcium, within the bile^[94].

3.2.2 Hormones

Estrogen, a ubiquitously occurring endogenous glycoside, assumes a pivotal physiological function in humans. Notably, excessive exposure to estrogen has long been acknowledged as a significant determinant in the pathogenesis of sex hormone-responsive disorders, with breast cancer (BCa) serving as a prime example^[95]. GUS enzymes play a cardinal role in the metabolic processes of endogenous hormones^[96], particularly those with estrogenic properties. Within the gut lumen, GUS enzymes catalyze the cleavage of estrogen-glucuronide conjugates, thereby liberating free hormonal forms. These liberated hormones subsequently enter the gut and systemic circulation, potentially culminating in abnormally elevated estrogen levels. The accumulation of such hormones is intimately correlated with the development of hormone-dependent neoplasms, such as breast cancer^[38], polycystic ovary syndrome^[97] and hepatocellular adenoma^[98].

3.2.3 Neurotransmitters

GUS enzymes play a role in the metabolism of neurotransmitters, including dopamine, norepinephrine, and serotonin, by influencing their bioavailability. The reactivation process mediated by GUS is a key step in regulating neurotransmitter levels. By hydrolyzing glucuronide conjugates, GUS enzymes release active, free neurotransmitters, potentially impacting intestinal motility, neurological function, and immune responses, and this process has also been implicated in the manifestation of psychiatric disorders, such as depression and anxiety. For instance, augmented GUS activity can lead to elevated levels of circulating serotonin, which then, induces diarrhea due to enhanced gastrointestinal motility and secretory function^[43]. Recent investigations have revealed that inhibition of GUS in conventional mice results in a reduction in free 5-hydroxytryptamine and an augmentation in its inactive glucuronide forms within both the serum and intestine^[99]. In contrast, elevated *in vivo* GUS activity is accompanied by increased levels of dopamine and norepinephrine, as well as enhanced intestinal motility^[11].

3.3 Toxicity of foodborne hazards mediated by GUS enzyme

3.3.1 Heterocyclic compound

The processing of meat and its exposure to heat can lead to a rise in the levels of compounds that may be carcinogenic, such as polycyclic aromatic hydrocarbons (PAHs) and HAAs, thereby increasing the risk of cancer. These compounds can lead to various types of cancer, including breast cancer, colon cancer,

etc.^[100,101]. Carcinogenic and mutagenic HAAs from food are metabolically activated in the body to form their respective N-hydroxy (OH)-arylamines. The N-glucuronidation of these metabolites is viewed as a crucial detoxification process. Research has indicated that liver microsomes are capable of catalyzing the glucuronidation of various heterocyclic amines, including 2-amino-3-methylimidazo [4,5-f] quinoline (IQ), 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP), 2-amino-6-methyl-dipyrimido [1,2-a:3',2'-d] imidazole (Glu-P-1), and 2-amino-3,8-dimethylimidazo [4,5-f] quinoline (MeIQx). Moreover, in the case of N-OH-PhIP, two microsomal N-glucuronide metabolites with different chemical and enzymatic properties are formed^[102]. UGT plays an important role in these detoxification metabolisms. The biological or chemical activity of glucuronic acid conjugates is lower than that of their corresponding aglycones. The polar and ionized carboxylic acid moiety of glucuronic acid facilitates the elimination of these conjugated metabolites from the body. However, some studies have found that 2-amino-9H-pyrido [2,3-b] indole (AaC) in tobacco smoke, after biotransformation, forms 2-hydroxyamino-9H-pyrido [2,3-b] indole (HONH-AaC), which can be activated by UGTs and is capable of reacting with proteins or DNA^[103,104].

Studies have found that gut microorganisms with GUS activity have the ability to hydrolyze PhIP-G to release PhIP. Gut microorganisms with glycerol/diol dehydratase (GDH) activity can cooperate to convert free PhIP into PhIP-M1. The combined activity of BGUS and GDH may be a potential factor in reducing mutagenicity^[44]. Further research is needed to fully understand the metabolic pathways of GUS-mediated heterocyclic compounds in the body, including their biotransformation, toxicity, and physiological impact.

3.3.2 Foodborne pathogenic bacteria

Foodborne pathogenic bacteria can cause bacterial diarrhea and acute gastroenteritis. For example, *Campylobacter jejuni* can cause bacterial diarrhea and acute gastroenteritis, and may also trigger sepsis, encephalitis, endocarditis, and urinary tract infections^[105]. *Staphylococcus aureus*, which can secrete toxins, is one of the most common causes of morbidity and mortality from infectious pathogens worldwide. This pathogen can cause a variety of diseases, leading to symptoms such as nausea, vomiting, regurgitation, and abdominal cramps. In more severe cases, it can even cause skin infections, fatal pneumonia, and sepsis^[106]. *Yersinia enterocolitica* can not only cause gastroenteritis, but also systemic diseases such as arthritis, myocarditis, subacute hepatitis, and even septicemia. Its mortality rate can reach 34%–50%^[107]. *Salmonella* is one of the high-risk factors affecting human health and is significantly distributed worldwide. However, the *Salmonella* genus has shown multidrug resistance to tetracyclines, kanamycin, sulfonamides, chloramphenicol, streptomycin, cephalosporins, and penicillin^[108]. Enterohemorrhagic *Escherichia coli* (EHEC) is a major foodborne pathogen that poses a serious public health threat. It specifically colonizes the large intestine and causes a variety of diseases. Enterohemorrhagic *E. coli* infection occurs after the ingestion of contaminated food and can lead to a range of conditions from mild watery diarrhea to hemorrhagic colitis and hemolytic-uremic syndrome^[109]. The invasion of foodborne pathogenic bacteria may disrupt the balance between probiotic bacteria and harmful bacteria in the intestine, leading to a decrease in probiotic bacteria and a large-scale proliferation of harmful bacteria. These harmful bacteria secrete a large amount of toxins, which affect the body's immunity and cause abdominal

distension, diarrhea, enteritis, and even various chronic metabolic diseases^[110].

The emergence of antimicrobial resistance in enteric bacterial pathogens transmitted through food is largely a result of antimicrobial usage in animals raised for food production. These medications are employed for therapeutic purposes, disease prevention, or as growth enhancers via feed additives. Despite regulations aimed at controlling antimicrobial use in livestock, resistance levels of non-typhoidal *Salmonella* and *Campylobacter* have significantly increased in developed nations in recent years^[111]. Therefore, it is crucial to develop new strategies to effectively combat pathogenic bacteria and address the rising issue of antimicrobial resistance. Recent studies have shown that inhibiting GUS and reducing the release of free glucuronic acid in the intestine can limit its uptake as a carbon source by intestinal pathogenic bacteria, thereby reducing their colonization^[6].

4 Key factors affecting the activity of GUS enzyme

The activity of GUS enzyme exhibits significant variations under different environments and conditions, and is regulated by a variety of internal and external factors. The following will explore in detail the main factors affecting the activity of GUS enzyme, including the composition of gut microbiota, dietary and environmental factors, host characteristics, and health status.

4.1 Composition and activity of gut microbiota

The composition of the gut microbiota has a significant impact on the activity of GUS enzyme. Different gut microbial populations possess distinct GUS enzyme subtypes and activity levels, and the dynamic changes of these microbial populations may directly affect the expression and function of GUS enzyme. The GUS enzyme subtypes (such as L1 type, L2 type, NL type, etc.) of different species in the gut microbiota have different substrate specificities and catalytic efficiencies. For example, *Bacteroides fragilis* and *Bacteroides dorei* predominantly express the acyclic (NL-type) GUS enzyme, which exhibits strong substrate hydrolysis capacity. In contrast, *Clostridium perfringens* and *Streptococcus agalactiae* mainly express the L1-type GUS enzyme, which demonstrates high catalytic activity toward small-molecule substrates^[31].

Gut microbiota dysbiosis (such as the overgrowth of *Clostridium difficile*) is often accompanied by changes in GUS enzyme activity. Dysbiosis may lead to the proliferation of certain pathogenic bacteria. The GUS enzymes produced by these bacterial species may increase the re-activation of drugs or endogenous metabolites, further exacerbating intestinal toxicity. For example, there is an association between gut microbiota dysbiosis and drug-induced toxicity, including drug-induced abdominal problems^[112].

4.2 Dietary factors

Food components, eating habits, and environmental pollutants can all affect the composition of the gut microbiota, thereby regulating the activity of GUS enzyme. A high-fat diet (especially animal fat) has been found to significantly increase the activity of GUS enzyme. Research shows that a high-fat diet may promote the proliferation of bacteria such as *Bacteroides*. The GUS enzymes produced by these bacteria have a high ability to hydrolyze glucuronic acid, thus enhancing the activation of drug

metabolites and hormones in the intestine^[113]. In addition, a high-protein diet can also increase the activity of GUS enzyme by promoting the growth of certain gut microbiota^[114]. While consumption of oat bran can reduce beta-glucuronidase^[115].

Prebiotics are substances that promote the growth of beneficial microorganisms. The prebiotic inulin significantly reduces the activity of β -glucosidase^[116]. Some studies have shown that probiotics and prebiotics can also alter the intestinal microbial community by increasing the concentration of beneficial bacteria such as lactic acid bacteria and *Bifidobacterium* and reducing the level of pathogenic microorganisms. They can bind to potential food carcinogens, inhibit β -glucuronidase to reduce the hydrolysis of precarcinogenic compounds, thereby reducing intestinal inflammation, enhancing immune function, and inhibiting the development and progression of tumors^[117]. *Lactobacillus plantarum* uses the prebiotic fructooligosaccharide (FOS) as a carbon source, inhibits the growth of pathogens that produce β -glucuronidase, and reduces its activity through the metabolites of FOS^[118]. It has also been shown that the use of probiotics protects the intestinal epithelium from microbiota dysbiosis and proliferative crypt damage, and also reduces β -glucuronidase expression and ROS significantly alleviating irinotecan-induced diarrhoea^[119].

Long-term use of certain drugs, such as antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs), can influence β -glucuronidase (GUS) activity^[84,120]. For instance, the use of antibiotics like vancomycin has been shown to significantly alter gut microbiota composition, leading to changes in GUS enzyme expression and subsequently affecting intestinal drug metabolism and toxic reactions^[84]. The use of NSAIDs can influence the composition and metabolic activity of the gut microbiota through direct effects on the microbiota (such as via inhibiting/promoting microbial growth, inducing microbial cell death and/or affecting microbial metabolism). For example, indomethacin has been shown to significantly induce the abundance of *Bacteroides* and *Enterobacteriaceae* bacteria^[53], both of which are GUS-producing bacterial genera^[31].

4.3 Host characteristics and health status

The physiological features of the host, namely age, sex, and genetic background, in addition to its health state, all exert a regulatory influence on the activity of GUS enzyme. Research findings have demonstrated that gender differences lead to variability in GUS enzyme activity. Specifically, males commonly possess higher GUS enzyme activity than females, a phenomenon that might be causally linked to the concentrations of sex hormones such as testosterone. In infants and toddlers, a notably elevated expression of GUS enzyme is detected within their gut flora, which plausibly stems from breastfeeding and the nascent formation of the gut microbiota^[121]. Both the gut microbiota and the activity of GUS enzyme are subject to age-related alterations. A specific study compared β -glucuronidase activity between adolescent male and female C57BL/6 mice and adult mice, analyzing potential age- and sex-related differences in enzyme expression and activity. The results revealed that as age advanced, there was a significant decline in female β -glucuronidase activity. Moreover, mice with diverse genetic backgrounds, like C57 and NIH-Swiss Webster, exhibited varying levels of β -glucuronidase activity, underlining the fact that host genetic diversity can also impact microbial metabolism^[122]. Some health conditions, particularly those affecting the gastrointestinal tract, can significantly alter the makeup of the gut microbiota. For example,

colon cancer patients were observed to have fecal β -glucuronidase activity that was 1.7 times higher than in healthy subjects. Notably, after sonicating the fecal samples, the enzyme activity in colon cancer patients increased dramatically to 12.1 times that of healthy controls^[123].

5 Toxicity abatement strategies targeting GUS enzymes

Recent studies suggest that targeted suppression of intestinal bacterial β -glucuronidase (β -GUS) activity can augment the effectiveness of anticancer drugs^[48]. Taking irinotecan as an example, its active metabolite, SN-38, undergoes glucuronidation for detoxification and is then excreted into the gastrointestinal tract. Here, intestinal bacteria exploit GUS to reconvert the glucuronidated metabolite back to the toxic SN-38, triggering diarrhea. By inhibiting GUS activity, this adverse side effect of irinotecan can be mitigated, loosening the dose constraints in anticancer drug administration and enhancing anticancer efficacy^[124]. GUS activity has recently been found to correlate with the severity of periodontitis and can be inhibited by the microbial GUS-selective inhibitor UNC4917^[125]. Evidence indicates that intestinal commensal microorganisms play a mediating role in the metabolic activation of triclosan (TCS) within the colon, spurring its enterotoxigenic effects. However, targeted inhibition of bacterial GUS enzymes can nullify the colitis-promoting impacts of TCS^[63]. In diarrhoeic renal transplant recipients treated with MMF post-transplant, diarrhoea was more prolonged in patients with higher faecal β -glucuronidase activity compared to those with lower faecal β -glucuronidase activity^[126]. Inhibition of GUS effectively prevents carcinogen-induced microflora dysbiosis and intestinal tumorigenesis^[127]. This all suggests that GUS enzymes can be used as targets for toxicity mitigation.

Effectual β -GUS inhibitors are capable of modulating intestinal bacterial β -GUS activity, consequently diminishing the intestinal toxicity of particular xenobiotics or warding off colon-related ailments. Inhibitors targeting bacterial β -glucuronidase have been found to modulate gut microbiota function without adversely affecting the host metabolic system^[128]. As a result, GUS inhibition has emerged as a novel strategy for disease management and drug treatment, attracting growing research attention. A wide range of inhibitor classes has been identified in existing studies, including flavonoids, alkaloids, quinolines, thiazoles, piperazines, and others (Table 2).

5.1 Inhibitor development

5.1.1 Medicines

In the development of GUS enzyme inhibitors, researchers have found that some existing drugs can also act as GUS enzyme modulators, such as antibiotics and some antidepressants.

The application of antibiotics has demonstrated certain advantages in alleviating β -GUS mediated drug toxicity within intestinal bacteria. For instance, vancomycin has been identified as effective in eradicating GUS-expressing bacteria in the gut^[147], subsequently reducing the conversion of MMF into the toxic metabolite mycophenolic acid (MPA)^[84]. Ciprofloxacin significantly reduces β -glucuronidase activity in the distal small intestine and ileocecum, thereby inhibiting diclofenac metabolism and reducing diclofenac-induced enteropathy^[146]. Similarly, the oral administration of streptomycin and penicillin, as well as neomycin and mycopeptide, which can nearly completely

suppress fecal β -glucuronidase activity, has been shown to alleviate irinotecan-induced weight loss and delay the onset of diarrhea symptoms^[13]. However, broad-spectrum antibiotics are generally used to eliminate a wide range of gut bacteria indiscriminately, potentially disrupting gut microbiota balance. Thus, while they do eliminate pathogenic bacteria, antibiotics also impact the commensal bacteria in the gut, triggering alterations in the composition and function of the gut microbiota, a condition referred to as dysbiosis. Extended use of antibiotics might precipitate long-term modifications in the gut microbiota, and these changes could potentially be linked to an elevated risk of a diverse array of diseases, encompassing allergic, metabolic, immune, and inflammatory disorders. Additionally, the gut microbiota may act as a reservoir for antibiotic resistance genes, and antibiotic use might accelerate the dissemination of these resistance genes^[148].

Studies investigating *E. coli* GUS enzyme inhibition have identified five key inhibitors: nicotinamide, isocarbazide, phenelzine, amoxapine, and mefloquine. The inhibitory activity of these compounds against endogenous GUS ranged from 17 nM to 7.1 μ M, while their IC₅₀ values for purified *E. coli* GUS spanned 71 nM to 2.3 μ M. Notably, among these inhibitors, nicotinamide, isocarbazide, and amoxapine demonstrated relatively lower activity against purified mammalian GUS, suggesting a degree of selectivity for bacterial GUS inhibition^[5].

5.1.2 Synthetic inhibitors

Currently, GUS inhibitors used in research primarily fall into two categories: synthetic inhibitors and naturally derived inhibitors. Among synthetic inhibitors, several classes have demonstrated *in vitro* inhibitory effects, including azamides^[149], Piperazines^[144], Quinolines^[141, 150], Thiazole derivatives^[151, 152], Pyrimidine derivatives^[153] and indoles^[154]. All show inhibitory effects *in vitro*. Among these, quinolines, azoles, and piperazines have attracted the most extensive research interest due to their potency and specificity in targeting GUS enzymes. Given that the active form of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38), bears resemblance to a quinoline analog, researchers have gone on to discover additional quinolines capable of inhibiting GUS enzymes through competitive inhibition. For illustration, when tumor-bearing mice were orally administered with 3-amino-4-(4-fluorophenylamino)-1H-pyrazolo[4, 3-c]quinoline in combination with the chemotherapeutic agent CPT-11, it not only averted the severe diarrhea induced by CPT-11 but also maintained the antitumor efficacy^[150]. Azoles constitute a class of five-membered aromatic heterocyclic compounds, invariably incorporating at least one nitrogen atom. Their structural rigidity and outstanding physicochemical attributes have made them a focal point of interest, endowing them with a broad spectrum of pharmacological activities and therapeutic prospects, thus rendering them prime targets for a multitude of synthetic studies. The azole family is characterized by a variety of compounds, including pyrazoles, imidazoles, thiazoles, triazoles, oxadiazoles, thiadiazoles, and tetrazoles, as well as their benzo counterparts like indoles, benzimidazoles, benzothiazoles, and benzotriazoles. These substances exhibit strong hydrogen bonding capabilities, primarily due to the presence of nitrogen and/or oxygen atoms in their ring structures, which facilitates more effective binding to biomolecular targets^[155]. For instance, certain thiazolidine-2-cyanamide derivatives demonstrated inhibitory activity against *E. coli* β -glucuronide glycosidase, exhibiting even more potent inhibition than the commonly employed positive control D-gluconolactone,

Table 2 Reported GUS inhibitors

Chemical type	Compound	Vivo/Vitro	IC ₅₀ (μM)	Reference
Flavonoids	Amentoflavone	Vitro	<i>E. coli</i> = 0.49 <i>C. perfringens</i> = 2.36, <i>S. pasteurii</i> = 2.88, <i>E. coli</i> = 3.43	[129, 130]
	Fisetin	Vitro	<i>E. coli</i> = 2.02	[131]
	Luteolin	Vitro	<i>E. coli</i> = 5.7, <i>S. pasteurii</i> = 5.5	[131]
	Icaritin	Vitro	<i>S. agalactiae</i> = 7.59	[131]
	Morin	Vitro	<i>S. pasteurii</i> = 8.36	[131]
	Quercetin	Vitro	<i>E. coli</i> = 4.91, <i>S. pasteurii</i> = 4.06	[131]
	Myricetin	Vitro	<i>E. coli</i> = 1.58, <i>S. pasteurii</i> = 9.25	[131]
	Hinokiflavone	Vivo(mice)	<i>E. elgens</i> = 0.09±0.01, <i>S. agalactiae</i> = 0.44 ± 0.01, <i>C. perfringens</i> = 0.2± 0.01, <i>E. coli</i> =0.69 ± 0.10	[132]
	Scutellarein	Vitro	<i>E. coli</i> = 5.76	[133]
	Demethoxydaibucarboline A	Vitro	-	[134]
Alkaloids	Berberine	Vivo(mice)	<i>E. coli</i> = 54.04 ± 5.104	[135]
	Grossamide	Vitro	<i>E. coli</i> = 0.73 ± 0.03, 1.24 ± 0.03	[136]
	Grossamide K Momordin IIa	Vitro		
Terpenoids	Hemslonin B	Vitro		
	3β-hydroxyolean-12-en-28-oic acid-28-O-β-D-glucopyranoside (6).	Vitro	<i>E. coli</i> = 8.3 ± 0.3, 1.0±0.1, 14.0 ± 1.3	[137]
	Euphominoid C	Vitro	<i>E. coli</i> = 45.87 ± 1.94	[138]
	Symplocitidins A Symplocitidins B	Vitro	<i>E. coli</i> = 30.8 ± 8.7, 17.2 ± 0.1	[139]
Quinolines	13, 19, 4, 12, 14, 22, 23, 25, 15, 8, 17, 11	Vitro	<i>E. coli</i> = 0.6 ± 0.45, 0.7 ± 0.12, 1.1 ± 0.05, 1.17 ± 0.12, 1.5 ± 0.05, 0.8 ± 0.11, 1.8 ± 0.02, 2.1 ± 0.07, 2.1 ± 0.06, 2.8 ± 0.05, 3.2 ± 0.11, 5.5 ± 0.14	[140]
	4, 8, 10, 12, 13, 14, 15, 20, 22	Vitro	<i>E. coli</i> =9.20±0.30, 6.70±0.25, 9.60±0.20, 3.10±0.10, 2.11±0.05, 5.01±0.20, 2.60±0.05, 9.60±0.20, 8.30±0.20	[141]
Azoles	1, 2, 3, 5, 7, 8	Vitro	<i>E. coli</i> = 5.7 ± 0.6, 1.2 ± 0.2, 4.7 ± 0.6, 7.3 ± 0.7, 9.3 ± 1.1, 6.1 ± 0.2	[142]
	7-21	Vitro	<i>E. coli</i> = 1.205 ± 0.105 - 0.082±0.001	[143]
Piperazines	UNC10201652	Vitro	<i>E. coli</i> = 0.108 ± 0.008, <i>E. elgens</i> = 0.127 ± 0.009, <i>C. perfringens</i> = 0.06 ± 0.01, <i>S. agalactiae</i> = 0.6 ± 0.2 <i>E. coli</i> = 0.800 ± 0.100,	[144]
	UNC4601	Vitro	<i>E. elgens</i> = 0.820 ± 0.040, <i>C. perfringens</i> = 0.900 ± 0.100, <i>S. agalactiae</i> = 2.400 ± 0.400 <i>E. coli</i> = 1.200 ± 0.800,	[144]
	UNC4511	Vitro	<i>E. elgens</i> =3.800 ± 0.300, <i>C. perfringens</i> = 2.000 ± 0.100, <i>E. coli</i> = 2.600 ± 0.400,	[144]
	UNC4540	Vitro	<i>C. perfringens</i> = 3.200 ± 0.600 <i>E. coli</i> = 0.100 ± 0.020,	[144]
	UNC10206579	Vitro	<i>E. elgens</i> = 0.123 ± 0.004, <i>C. perfringens</i> = 0.032 ± 0.002, <i>S. agalactiae</i> = 0.300 ± 0.030 <i>E. coli</i> = 0.070 ± 0.010,	[144]
	UNC10206577	Vitro	<i>E. elgens</i> = 0.118 ± 0.004, <i>C. perfringens</i> = 0.049 ± 0.002, <i>S. agalactiae</i> = 0.700 ± 0.090 <i>E. coli</i> = 0.029 ± 0.006,	[144]
	UNC10206581	Vitro	<i>E. elgens</i> = 0.088 ± 0.008, <i>C. perfringens</i> = 0.034 ± 0.002, <i>S. agalactiae</i> = 0.770 ± 0.090	[144]
Drugs	Amoxapine	Vitro	<i>E. coli</i> = 0.34	[145]
	Ciprofloxacin	Vitro	<i>E. coli</i> = 27.06	[146]

with IC₅₀ values spanning from 1.2 μM to 23.1 μM^[142]. The (E)-4-aryl-2-(2-(pyren-1-ylmethylene) hydrazinyl) thiazole derivatives were subjected to in vitro β-glucuronidase inhibitory activity assays, and all the molecules manifested excellent inhibition, with IC₅₀ = 3.10 ± 0.10-40.10 ± 0.90 μM^[151]. Investigators also evaluated a series of indole analogs for their β-glucuronidase inhibitory activity, and the majority of the compounds were identified with IC₅₀ values ranging from 0.50 to 53.40 μM^[156]. Piperazine-containing GUS inhibitors, which are selective for microbial GUS

enzymes, operate by intercepting the catalytic intermediates of glycosylases to inhibit GUS^[157].

Novel hybrid frameworks combining disulfide and sulfoxide moieties have also been synthesized and function as β-glucuronidase inhibitors^[158]. In the recent past, certain urea derivatives, which have been newly synthesized, have been discovered to possess inhibitory effects on GUS^[159]. Additionally, some metal complexes have likewise been found to exhibit GUS inhibitory capabilities^[149].

5.1.3 Inhibitors of Food and Medicine Homologous and Other Natural

On the other hand, natural compounds derived from medicinal plants represent a valuable reservoir for identifying lead compounds or potential drug candidates for GUS inhibition. These naturally occurring inhibitors offer promising therapeutic potential, often with favorable safety profiles and bioavailability, making them an important focus in drug discovery. For example, it has been observed that octyl gallate (OG) can markedly reduce BGUS activity without perturbing the overall fecal microbiome of mice. Moreover, when administered, OG effectively mitigated gastrointestinal toxicity and systematically reversed the colitis phenotype in a model of MMF-induced colitis^[56]. The cypress and its principal constituent, amphioxanthone (AMF), also demonstrated inhibitory activity against *Escherichia coli* GUS^[129]. Hibiscus alkaloids have likewise been shown to impede β -glucuronidase^[136]. Over the past decades, the inhibitory effects of natural chemotaxis on GUS have been reported for a variety of structures, including flavonoids^[133], terpenoids^[160], and various derivatives^[161]. Among them, flavonoid inhibitors have been the most prevalently reported. In a conformational relationship analysis concerning the discovery of flavonoid inhibitors, it was revealed that multiple flavonoids (including baicalein, lignans, baicalein, baicalein, quercetin, and baicalein) exerted strong to moderate inhibition on EcoGUS. In contrast, isoflavones and dihydroflavonoids exhibited only weak inhibitory effects on EcoGUS, and flavonoids lacking glucosyl or methoxyl modifications were highly inhibitory to EcoGUS^[133]. Picrasinol X, azurin, 5,7,2'-trihydroxy-8,6'-dimethoxyflavone, desmethylbellidinomycin, and gentianin were found to possess potent inhibitory effects on EcoGUS^[162]. Several medicinal compounds have also been ascertained to possess GUS inhibitory properties. A diet supplemented with raspberry pomace significantly augmented the colon and plasma levels of total ellagitannin metabolites while diminishing β -glucuronidase activity^[163]. Eight compounds were isolated from the stems of *Sphaerandra*, a medicinal plant of the genus *Schisandra*. Among these, a new triterpenoid was isolated that manifested potent inhibitory effects on α -glucosidase (AGS) as well as bacterial β -glucosidase^[164].

5.2 Challenges and prospects

5.2.1 Challenges

Commercially available β -glucuronidase inhibitors, such as D-Saccharic acid 1,4-lactone hydrate, have only been confirmed to inhibit *E. coli* GUS (EcoGUS), with an IC_{50} value of 48.4 μ M. Meanwhile, other β -glucuronidase inhibitors with higher potency, such as *Ganoderma lucidum* enoic acid A, are often cost-prohibitive, limiting their widespread use in research and therapeutic applications. In the current body of research regarding synthetic inhibitors, despite extensive efforts in synthesizing a vast array of new inhibitors and achieving a comprehensive exploration of synthetic inhibitor development, there remains a dearth of in vivo validation and other crucial aspects. Consequently, it remains an arduous task to translate synthetic inhibitors from the laboratory bench to practical clinical applications. Given the increasing cases of GUS-mediated toxicity, there is an urgent need for a rapidly deployable GUS inhibition strategy. While certain existing drugs have been identified with GUS inhibitory properties^[5], further research is necessary to

determine whether combining these drugs could lead to additional adverse effects. Additionally, using antibiotics to reduce GUS activity in the intestinal tract poses a high risk of inducing dysbiosis, potentially disrupting gut microbiota balance and leading to unintended health consequences.

Existing inhibitors are mostly screened using only EcoGUS. Although EcoGUS is one of the most predominant GUS in the intestine, the abundance of intestinal flora changes under different disease conditions, the GUS involved in metabolic processes may be different in different pathological states, and the GUS is also involved in the metabolism of endogenous compounds in the body, which maintain the daily physiological activities. There are many GUS in the intestine, and their structures and activities are very complex. Therefore, the discovery of GUS enzymes that plays a role in specific pathological processes as well as target-specific inhibitors is important for the efficient utilization of inhibitors and the maintenance of normal physiological activities. The discovery of GUS enzymes for specific physiopathological processes using techniques such as ABPP and the discovery of effective inhibitors through high-throughput drug screening may be an avenue for GUS enzyme research in the future.

Currently, GUS inhibition strategies are primarily applied to mitigate intestinal toxicity caused by anticancer drugs, NSAIDs, and other pharmaceuticals. However, the broader pathological roles of GUS enzymes remain largely unexplored. Future research could integrate hepatic metabolism studies to identify metabolites capable of forming glucuronidation glycoside conjugates. Additionally, further investigation is needed to discover compounds activated by GUS during metabolism, which could provide new insights into drug interactions, toxicity mechanisms, and potential therapeutic targets. Linking these glycosides, which can be metabolized by GUS, to physiological states reveals more of the roles played by GUS in the human body. A key challenge for future research is establishing a one-to-one relationship between disease states, specific GUS enzymes, and their corresponding inhibitors to enable precise and targeted inhibition. Identifying disease-specific GUS isoforms and designing selective inhibitors tailored to each condition will be critical in minimizing off-target effects while maximizing therapeutic efficacy. This approach requires a deeper understanding of GUS enzyme variations, their substrate specificities, and their role in different pathological processes, paving the way for more personalized and effective treatments.

5.2.2 Prospects

The intestinal toxicity mediated by GUS enzyme manifests in diverse forms, spanning from chemotherapeutic agents like irinotecan to commonly used NSAIDs in daily life, and even to dietary carcinogens. Given this variability, a generalized therapeutic approach may be more suitable to accommodate diverse populations, ensuring broader efficacy and accessibility across different disease states and patient demographics. However, future advancements in precision medicine may help refine targeted GUS inhibition strategies for more individualized treatments. Moreover, in recent years, as most edible herbs and fruits have showcased a satisfactory safety record over a long history of medical application, and owing to the inherent qualities of being suitable for daily and long-term use that medicinal herbs possess, such herbals may effectively address the needs of different individuals. For patients using chemotherapy drugs, it can alleviate the burden of drug intake: for those relying on NSAIDs for an extended period, it can cater to their specific requirements: and for

people who frequently consume fried and smoked foods, it can be incorporated into their daily routine. As a result, a growing number of researchers are focusing on the discovery of natural inhibitors derived from phytochemicals found in edible herbs and fruits, which may offer a safer and more accessible alternative for GUS inhibition. Typically, natural inhibitors originate from ordinary plants, such as herbs and spice plants. By extracting their active constituents, substances with inhibitory capabilities can be procured and assessed. Since they are sourced from natural products, they are less prone to inducing side effects within the body and are likely comparatively safer than synthetic inhibitors. Numerous natural inhibitors exhibit a broad spectrum of inhibitory actions. It has been observed that certain natural products, like amentoflavone derived from *Ginkgo biloba*, display potent inhibitory effects on a wide array of GUS enzymes and can serve as promising precursor compounds for the development of novel drugs aimed at mitigating GUS-associated intestinal toxicity^[130]. A substantial number of studies have documented the inhibitory impacts of active ingredients in medicinal substances on GUS (Table 3). As the mechanism of action of natural inhibitors differs from that of conventional antibiotics, they are less likely to trigger bacterial resistance. Natural inhibitors are derived from renewable resources, making them a sustainable option for drug development. Their production and utilization typically have a low environmental impact, offering an eco-friendly alternative to synthetic inhibitors. Moreover, many natural inhibitors are readily degradable in nature and do not lead to long-term environmental pollution, which aligns with the principles of green and sustainable development. Most importantly, beyond their GUS inhibitory properties, many natural inhibitors exhibit a range of beneficial biological activities, including anti-inflammatory, antioxidant, and wound-healing effects, making them promising candidates for multifunctional therapeutic applications.

The underlying mechanism of the intestinal toxicity induced by anticancer drugs and NSAIDs hinges on the fact that GUS hydrolysis acts upon drug-glucuronide-coupled compounds, which have been converted into an inactive form by the UGT enzyme. This process liberates glycosides, and when a significant accumulation of these glycosides occurs in the intestine, it culminates in enterotoxicity. Conventionally, the mitigation strategy has been to relieve enterotoxicity by suppressing GUS activity and curtailing the release of glycosides. Nevertheless, one of the most remarkable attributes of natural inhibitors is their

versatility. Not only can they function as GUS inhibitors, but a substantial number of them also possess a diverse range of biological activities, such as anti-inflammatory, antioxidant, and promotion of wound healing capabilities. Hence, even after fulfilling their role as GUS inhibitors, the inherent biological activities of natural inhibitors can continue to exert additional beneficial effects within the gut. In a recent investigation, dehydrodiisoeugenol (DDIE) isolated from nutmeg was discovered to confer multiple benefits. It was found to ameliorate weight loss, colon shortening, epithelial barrier dysfunction, depletion of goblet cells and intestinal stem cells (ISCs), as well as enhance wound healing. Simultaneously, DDIE counteracted the CPT11-induced proliferation of *Enterococcus faecalis*, which in turn led to a reduction in the intestinal levels of Gus and SN38. This attenuation of CPT11-induced intestinal mucositis was accompanied by a synergistic effect with CPT-11 in terms of antitumor activity^[167]. This example vividly illustrates the multifaceted therapeutic potential of natural inhibitors when employed as GUS inhibitors, since they are capable of intervening at various stages of the disease process.

Generally speaking, the development of natural inhibitors, particularly those natural compounds derived from medicinal herbs, holds extensive promise. China is abundantly endowed with medicinal herb resources that share the same origin as food, laying a solid groundwork for research and exhibiting a remarkable potential for exploration. The diverse array of natural compounds from these food-medicine homologous medicinal herbs encompasses flavonoids, terpenoids, alkaloids, and the like. Currently, while research has explored the potential of natural compounds as GUS inhibitors, a large number of bioactive resources remain underexplored and undeveloped, highlighting the need for further investigation and utilization. Therefore, the pursuit of obtaining highly efficient GUS inhibitors, as well as broad-spectrum or specific GUS inhibitors, has emerged as the critical research direction. Among the available methodologies, virtual high-throughput drug screening (vHTS) has proven to be an efficacious means for targeted drug discovery^[171]. Probes for GUS activity assays have also been developed^[172]. Recent studies have increasingly focused on identifying GUS enzymes involved in specific physiopathological processes using techniques such as activity-based protein profiling (ABPP). Additionally, researchers are working on developing targeted inhibition strategies to selectively modulate GUS activity in disease-specific contexts^[99].

Table 3 Inhibition of GUS by active ingredients in medicinal foods and herbs

Plants	Compound	Vivo/Vitro	IC ₅₀ (μM)	References
<i>Ganoderma lucidum</i>	Ganoderenic acid A	Vitro	<i>E. coli</i> = 0.07 mg/mL	[165]
<i>Raspberry</i>	Ellagitannins Anthocyanins	Vivo (Wistar rats)	-	[163]
<i>Zanthoxylum piperitum</i>	Zanthopiperitol (1), Ailanthoidiol (2), 5-benzofuranpropanol (3), 2-propen-1-ol (4), Demethoxywutaensol methyl ether (5)	Vitro	<i>E. coli</i> = 68.39 ± 2.29 (2)	[166]
<i>Nutmeg</i>	Dehydrodiisoeugenol	Vivo (mice)	-	[167]
<i>Pueraria thunbergiana</i>	Tectorigenin	Vivo (mice)	<i>E. coli</i> = 0.3 mg/mL	[168]
<i>Glycyrrhiza uralensis</i>	Glycyrrhizin	Vivo (Wistar rats)	<i>E. coli</i> = 0.01 mg/mL <i>E. coli</i> = 0.24 mg/mL	[169]
<i>Astragalus membranaceus</i>	18β-Glycyrrhetic Acid Astraoleanoside H Cloversaponin III	Vitro	<i>E. coli</i> = 21.20 ± 0.75 <i>E. coli</i> = 9.05 ± 0.47 EcoGUS = 0.4 ± 0.1, 1.6 ± 0.1 <i>E. coli</i> 3L3 = 33.2 ± 5.2, 8.5 ± 0.5	[160]
<i>Mulberry</i>	Sanggenon C Kuwanon G	Vitro	<i>E. fergusonii</i> 3G4 = 10.4 ± 2.1, 7.5 ± 0.4 <i>S. pasteurii</i> 3I10 = 17.6 ± 0.6, 14.5 ± 0.9 SpasGUS = 0.33 ± 0.05, 0.98 ± 0.25	[170]

6 Conclusion

Synthetic compounds present significant challenges for clinical application, including issues related to safety, specificity, and side effects. In response to the growing demand for GUS inhibitors in clinical settings, natural inhibitors, particularly those derived from medicinal herbs, have emerged as the most promising solution. However, the screening and development of natural compounds remain incomplete, and many bioactive compounds have yet to be fully explored.

Furthermore, while GUS enzymes play crucial roles in various physiological processes, many of their functions remain poorly understood, and their involvement in additional physiological and pathological pathways is an area ripe for further research.

Advancements in metagenomic sequencing, bacterial cultivation, and virtual screening have become key drivers in the identification of GUS inhibitors, facilitating the discovery of new therapeutic targets. However, the process of pinpointing specific GUS enzymes involved in particular deconjugation reactions is still in its early stages, requiring further investigation and refinement. Until recently, most studies on GUS inhibition have primarily been conducted in vitro or using animal models, which do not always directly translate to clinical applications. Creating GUS inhibitors with significant pharmacological properties is crucial for mitigating the toxicity caused by GUS during targeted drug treatments.

Finally, to identify effective inhibitors from a vast pool of compounds and to elucidate the role of GUS in specific physiological processes, computational approaches could also provide an efficient and systematic solution. Techniques such as molecular docking, virtual screening, machine learning, and AI-driven drug discovery can accelerate the identification of promising GUS inhibitors and improve our understanding of enzyme-substrate interactions, paving the way for targeted therapeutic strategies.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work. Chongjiang Cao is an Editorial Board Member of Food & Medicine Homology, but was not involved in the processing, peer review or decision making of this article.

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References

- Ahlatwat, S., Asha, Sharma, K. K. Gut-organ axis: A microbial outreach and networking. *Letters in Applied Microbiology*, **2021**, 72: 636–668. <https://doi.org/10.1111/lam.13333>
- Chen, J., Li, Y., Tang, S., et al. Gut microbial β -glucuronidases and their role in the microbiome-metabolite axis in colorectal cancer. *Nature Communications*, **2025**, 16: 10660. <https://doi.org/10.1038/s41467-025-65679-y>
- Visconti, A., Le Roy, C. I., Rosa, F., et al. Interplay between the human gut microbiome and host metabolism. *Nature Communications*, **2019**, 10: 4505. <https://doi.org/10.1038/s41467-019-12476-z>
- Chamseddine, A. N., Ducreux, M., Armand, J. P., et al. Intestinal bacterial β -glucuronidase as a possible predictive biomarker of irinotecan-induced diarrhea severity. *Pharmacology & Therapeutics*, **2019**, 199: 1–15. <https://doi.org/10.1016/j.pharmthera.2019.03.002>
- Ahmad, S., Hughes, M. A., Yeh, L. A., et al. Potential repurposing of known drugs as potent bacterial β -glucuronidase inhibitors. *SLAS Discovery*, **2012**, 17: 957–965. <https://doi.org/10.1177/1087057112444927>
- Rosay, T., Jimenez, A. G., Sperandio, V. Glucuronic acid confers colonization advantage to enteric pathogens. *Proceedings of the National Academy of Sciences of the United States of America*, **2024**, 121: e2400226121. <https://doi.org/10.1073/pnas.2400226121>
- Wallace, B. D., Wang, H., Lane, K. T., et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. *Science*, **2010**, 330: 831–835. <https://doi.org/10.1126/science.1191175>
- Ervin, S. M., Hanley, R. P., Lim, L., et al. Targeting regorafenib-induced toxicity through inhibition of gut microbial β -glucuronidases. *ACS Chemical Biology*, **2019**, 14: 2737–2744. <https://doi.org/10.1021/acschembio.9b00663>
- Vyas, V. D., Parameswaran, S. A., Paramasivan, P., et al. Etiological profile of diarrhea in solid organ transplant recipients at a tertiary care center in southern India. *Transplant Infectious Disease*, **2021**, 23: e13584. <https://doi.org/10.1111/tid.13584>
- Sudo, N. Biogenic amines: signals between commensal microbiota and gut physiology. *Frontiers in Endocrinology*, **2019**, 10: 504. <https://doi.org/10.3389/fendo.2019.00504>
- Asano, Y., Hiramoto, T., Nishino, R., et al. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **2012**, 303: G1288–G1295. <https://doi.org/10.1152/ajpgi.00341.2012>
- Michaud, J. E., Partin, A. W. Testosterone and prostate cancer: an evidence-based review of pathogenesis and oncologic risk. *Therapeutic Advances in Urology*, **2015**, 7: 378–387. <https://doi.org/10.1177/1756287215597633>
- Takasuna, K., Hagiwara, T., Watanabe, K., et al. Optimal antidiarrhea treatment for antitumor agent irinotecan hydrochloride (CPT-11)-induced delayed diarrhea. *Cancer Chemother Pharmacol*, **2006**, 58: 494–503. <https://doi.org/10.1007/s00280-006-0187-8>
- Whittle, B. J. R. Gastrointestinal effects of nonsteroidal anti-inflammatory drugs. *Fundamental & Clinical Pharmacology*, **2003**, 17: 301–313. <https://doi.org/10.1046/j.1472-8206.2003.00135.x>
- Malfatti, M. A., Ubick, E. A., Felton, J. S. The impact of glucuronidation on the bioactivation and DNA adduction of the cooked-food carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in vivo. *Carcinogenesis*, **2005**, 26: 2019–2028. <https://doi.org/10.1093/carcin/bgi151>
- Simpson, J. B., Walker, M. E., Sekela, J. J., et al. Gut microbial β -glucuronidases influence endobiotic homeostasis and are modulated by diverse therapeutics. *Cell Host & Microbe*, **2024**, 32: 925–944.e10. <https://doi.org/10.1016/j.chom.2024.04.018>
- Sudan, C., Prakash, S., Bhomkar, P., et al. Ubiquitous presence of β -glucuronidase (GUS) in plants and its regulation in some model plants. *Planta*, **2006**, 224: 853–864. <https://doi.org/10.1007/s00425-006-0276-2>
- Gartland, K. M. A., McHugh, A. T., Vitha, S., et al. Analysis of genetically modified plant gene expression using GUS fluorimetry. *Molecular Biotechnology*, **2000**, 14: 235–239. <https://doi.org/10.1385/MB:14:3:235>
- Koburger, J. A., Miller, M. L. Evaluation of a fluorogenic MPN procedure for determining *Escherichia coli* in oysters. *Journal of Food Protection*, **1985**, 48: 244–245. <https://doi.org/10.4315/0362-028X-48.3.244>
- Levy, G. A., Marsh, C. A. Preparation and properties of β -glucuronidase. *Advances in Carbohydrate Chemistry*, **1959**, 14: 381–428. [https://doi.org/10.1016/S0096-5332\(08\)60227-1](https://doi.org/10.1016/S0096-5332(08)60227-1)
- Sebastiano, M., D'Alessio, M., Bazzicalupo, P. β -glucuronidase

- mutants of the nematode *Caenorhabditis elegans*. *Genetics*, **1986**, 112: 459–468.
- [22] Langley, S. D., Wilson, S. D., Gross, A. S., et al. A genetic variant of beta-glucuronidase in *Drosophila melanogaster*. *Journal of Biological Chemistry*, **1983**, 258: 7416–7424. [https://doi.org/10.1016/S0021-9258\(18\)32195-1](https://doi.org/10.1016/S0021-9258(18)32195-1)
- [23] Swank, R. T., Pfister, K., Miller, D., et al. The egasyn gene affects the processing of oligosaccharides of lysosomal beta-glucuronidase in liver. *Biochemical Journal*, **1986**, 240: 445–454. <https://doi.org/10.1042/bj2400445>
- [24] Zhu, B. T., Evaristus, E. N., Antoniuk, S. K., et al. Metabolic deglucuronidation and demethylation of estrogen conjugates as a source of parent estrogens and catecholesterogen metabolites in Syrian hamster kidney, a target organ of estrogen-induced tumorigenesis. *Toxicology and Applied Pharmacology*, **1996**, 136: 186–193. <https://doi.org/10.1006/taap.1996.0023>
- [25] Zhou, X., Wang, D., Gao, Z., et al. Highly sensitive light-up near-infrared fluorescent probe for detection and imaging of β -glucuronidase in human serum, living cells and tumor-bearing mice. *Science China Materials*, **2022**, 65: 836–844. <https://doi.org/10.1007/s40843-021-1779-7>
- [26] Gloux, K., Berteau, O., Oumami, H. E., et al. A metagenomic β -glucuronidase uncovers a core adaptive function of the human intestinal microbiome. *Proceedings of the National Academy of Sciences of the United States of America*, **2011**, 108: 4539–4546. <https://doi.org/10.1073/pnas.100066107>
- [27] Nakamura, J., Kubota, Y., Miyaoka, M., et al. Comparison of four microbial enzymes in clostridia and bacteroides isolated from human feces. *Microbiology and Immunology*, **2002**, 46: 487–490. <https://doi.org/10.1111/j.1348-0421.2002.tb02723.x>
- [28] Russell, W. M., Klaenhammer, T. R. Identification and cloning of *gusA*, encoding a new β -glucuronidase from *Lactobacillus Gasseri* ADH. *Applied and Environmental Microbiology*, **2001**, 67: 1253–1261. <https://doi.org/10.1128/AEM.67.3.1253-1261.2001>
- [29] Michikawa, M., Ichinose, H., Momma, M., et al. Structural and biochemical characterization of glycoside hydrolase family 79 β -glucuronidase from *Acidobacterium Capsulatu*. *Journal of Biological Chemistry*, **2012**, 287: 14069–14077. <https://doi.org/10.1074/jbc.M112.346288>
- [30] McBain, A. J., Macfarlane, G. T. Ecological and physiological studies on large intestinal bacteria in relation to production of hydrolytic and reductive enzymes involved in formation of genotoxic metabolites. *Journal of Medical Microbiology*, **1998**, 47: 407–416. <https://doi.org/10.1099/00222615-47-5-407>
- [31] Pollet, R. M., D'Agostino, E. H., Walton, W. G., et al. An atlas of β -glucuronidases in the human intestinal microbiome. *Structure*, **2017**, 25: 967–977.e5. <https://doi.org/10.1016/j.str.2017.05.003>
- [32] Dabek, M., McCrae, S. I., Stevens, V. J., et al. Distribution of β -glucosidase and β -glucuronidase activity and of β -glucuronidase gene *gus* in human colonic bacteria. *FEMS Microbiology Ecology*, **2008**, 66: 487–495. <https://doi.org/10.1111/j.1574-6941.2008.00520.x>
- [33] Pellock, S. J., Walton, W. G., Biernat, K. A., et al. Three structurally and functionally distinct β -glucuronidases from the human gut microbe *Bacteroides uniformis*. *Journal of Biological Chemistry*, **2018**, 293: 18559–18573. <https://doi.org/10.1074/jbc.RA118.005414>
- [34] Pellock, S. J., Walton, W. G., Ervin, S. M., et al. Discovery and characterization of FMN-binding β -glucuronidases in the human gut microbiome. *Journal of Molecular Biology*, **2019**, 431: 970–980. <https://doi.org/10.1016/j.jmb.2019.01.013>
- [35] Hou, Y., Wu, H., Zhang, Z., et al. *Bacteroides intestinalis* mediates the sensitivity to irinotecan toxicity via tryptophan catabolites. *Gut*, **2025**, 334699. <https://doi.org/10.1136/gutjnl-2024-334699>
- [36] Cheng, K. W., Tseng, C. H., Tzeng, C. C., et al. Pharmacological inhibition of bacterial β -glucuronidase prevents irinotecan-induced diarrhea without impairing its antitumor efficacy in vivo. *Pharmacological Research*, **2019**, 139: 41–49. <https://doi.org/10.1016/j.phrs.2018.10.029>
- [37] Boelsterli, U. A., Redinbo, M. R., Saitta, K. S. Multiple NSAID-induced hits injure the small intestine: underlying mechanisms and novel strategies. *Toxicological Sciences*, **2013**, 131: 654–667. <https://doi.org/10.1093/toxsci/kfs310>
- [38] Sui, Y., Wu, J., Chen, J. The role of gut microbial β -glucuronidase in estrogen reactivation and breast cancer. *Frontiers in Cell and Developmental Biology*, **2021**, 9: 631552. <https://doi.org/10.3389/fcell.2021.631552>
- [39] O'Mahony, S. M., Clarke, G., Borre, Y. E., et al. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*, **2015**, 277: 32–48. <https://doi.org/10.1016/j.bbr.2014.07.027>
- [40] Ruddick, J. P., Evans, A. K., Nutt, D. J., et al. Tryptophan metabolism in the central nervous system: medical implications. *Expert Reviews in Molecular Medicine*, **2006**, 8: 1–27. <https://doi.org/10.1017/S1462399406000068>
- [41] O'Neill C. Gut microbes metabolize parkinson's disease drug. *Science*, **2019**, 364: 1030–1031. <https://doi.org/10.1126/science.aax8937>
- [42] Skar, V., Skar, A. G., Bratlie, J., et al. Beta-glucuronidase activity in the bile of gallstone patients both with and without duodenal diverticula. *Scandinavian Journal of Gastroenterology*, **1989**, 24: 205–212. <https://doi.org/10.3109/00365528909093038>
- [43] Pellock, S. J., Redinbo, M. R. Glucuronides in the gut: sugar-driven symbioses between microbe and host. *Journal of Biological Chemistry*, **2017**, 292: 8569–8576. <https://doi.org/10.1074/jbc.R116.767434>
- [44] Zhang, J., Lacroix, C., Wortmann, E., et al. Gut microbial beta-glucuronidase and glycerol/diol dehydratase activity contribute to dietary heterocyclic amine biotransformation. *BMC Microbiology*, **2019**, 19: 99. <https://doi.org/10.1186/s12866-019-1483-x>
- [45] Jeong, Y., Han, X., Vyas, K., et al. Microbial β -glucuronidase hydrogel beads activate chemotherapeutic prodrug. *ACS Applied Materials & Interfaces*, **2024**, 16: 28093–28103. <https://doi.org/10.1021/acsami.4c02568>
- [46] Holmes, E., Li, J. V., Athanasiou, T., et al. Understanding the role of gut microbiome–host metabolic signal disruption in health and disease. *Trends in Microbiology*, **2011**, 19: 349–359. <https://doi.org/10.1016/j.tim.2011.05.006>
- [47] Wallace, B. D., Roberts, A. B., Pollet, R. M., et al. Structure and inhibition of microbiome β -glucuronidases essential to the alleviation of cancer drug toxicity. *Chemistry & Biology*, **2015**, 22: 1238–1249. <https://doi.org/10.1016/j.chembiol.2015.08.005>
- [48] Bhatt, A. P., Pellock, S. J., Biernat, K. A., et al. Targeted inhibition of gut bacterial β -glucuronidase activity enhances anticancer drug efficacy. *Proceedings of the National Academy of Sciences of the United States of America*, **2020**, 117: 7374–7381. <https://doi.org/10.1073/pnas.1918095117>
- [49] Watanabe, T., Tanigawa, T., Shiba, M., et al. Anti-tumour necrosis factor agents reduce non-steroidal anti-inflammatory drug-induced small bowel injury in rheumatoid arthritis patients. *Gut*, **2014**, 63: 409–414. <https://doi.org/10.1136/gutjnl-2013-304713>
- [50] Tobin, P. J., Seale, P., Lee, S., et al. The in vitro metabolism of irinotecan (CPT-11) by carboxylesterase and β -glucuronidase in human colorectal tumours. *Journal of Clinical Oncology*, **2006**, 62: 122–129. https://doi.org/10.1200/jco.2005.23.16_suppl.3650
- [51] Guthrie, L., Gupta, S., Daily, J., et al. Human microbiome signatures of differential colorectal cancer drug metabolism. *NPJ Biofilms Microbiomes*, **2017**, 3: 27. <https://doi.org/10.1038/s41522-017-0034-1>
- [52] Dashnyam, P., Mudududda, R., Hsieh, T. J., et al. β -glucuronidases of opportunistic bacteria are the major contributors to xenobiotic-induced toxicity in the gut. *Scientific Reports*, **2018**, 8: 16372. <https://doi.org/10.1038/s41598-018-34678-z>
- [53] Terán-Ventura, E., Aguilera, M., Vergara, P., et al. Specific changes of gut commensal microbiota and TLRs during Indomethacin-induced acute intestinal inflammation in rats. *Journal*

- of Crohn's and Colitis, **2014**, 8: 1043–1054. <https://doi.org/10.1016/j.crohns.2014.02.001>
- [54] Saïtta, K. S., Zhang, C., Lee, K. K., et al. Bacterial β -glucuronidase inhibition protects mice against enteropathy induced by indomethacin, ketoprofen or diclofenac: mode of action and pharmacokinetics. *Xenobiotica*, **2014**, 44: 28–35. <https://doi.org/10.3109/00498254.2013.811314>
- [55] Romberg, R. W., Lee, L. Comparison of the hydrolysis rates of morphine-3-glucuronide and morphine-6-glucuronide with acid and β -glucuronidase. *Journal of Analytical Toxicology*, **1995**, 19: 157–162. <https://doi.org/10.1093/jat/19.3.157>
- [56] Xia, L. J., Wan, L., Gao, A., et al. Targeted inhibition of gut bacterial β -glucuronidases by octyl gallate alleviates mycophenolate mofetil-induced gastrointestinal toxicity. *International Journal of Biological Macromolecules*, **2024**, 264: 130145. <https://doi.org/10.1016/j.ijbiomac.2024.130145>
- [57] Viték, L., Majer, F., Muchová, L., et al. Identification of bilirubin reduction products formed by *Clostridium Perfringens* isolated from human neonatal fecal flora. *Journal of Chromatography B*, **2006**, 833: 149–157. <https://doi.org/10.1016/j.jchromb.2006.01.032>
- [58] Tiribelli, C., Ostrow, J. D. Intestinal flora and bilirubin. *Journal of Hepatology*, **2005**, 42: 170–172. <https://doi.org/10.1016/j.jhep.2004.12.002>
- [59] Ervin, S. M., Li, H., Lim, L., et al. Gut microbial β -glucuronidases reactivate estrogens as components of the estrobolome that reactivate estrogens. *Journal of Biological Chemistry*, **2019**, 294: 18586–18599. <https://doi.org/10.1074/jbc.RA119.010950>
- [60] Legan, T. B., Lavoie, B., Mawe, G. M. Direct and indirect mechanisms by which the gut microbiota influence host serotonin systems. *Neurogastroenterol Motil*, **2022**, 34: e14346. <https://doi.org/10.1111/nmo.14346>
- [61] Humblot, C., Murkovic, M., Rigottier-Gois, L., et al. β -Glucuronidase in human intestinal microbiota is necessary for the colonic genotoxicity of the food-borne carcinogen 2-amino-3-methylimidazo[4,5-f]quinoline in rats. *Carcinogenesis*, **2007**, 28: 2419–2425. <https://doi.org/10.1093/carcin/bgm170>
- [62] Alexander, J., Wallin, H., Rossland, O. J., et al. Formation of a glutathione conjugate and a semistable transportable glucuronide conjugate of n2-oxidized species of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (phip) in rat liver. *Carcinogenesis*, **1991**, 12: 2239–2245. <https://doi.org/10.1093/carcin/12.12.2239>
- [63] Zhang, J., Walker, M. E., Sanidad, K. Z., et al. Microbial enzymes induce colitis by reactivating triclosan in the mouse gastrointestinal tract. *Nature Communications*, **2022**, 13: 136. <https://doi.org/10.1038/s41467-021-27762-y>
- [64] Conroy, T., Desseigne, F., Ychou, M., et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New England Journal of Medicine*, **2011**, 364: 1817–1825. <https://doi.org/10.1056/NEJMoa1011923>
- [65] Pommier, Y. Topoisomerase I inhibitors: camptothecins and beyond. *Nature Reviews Cancer*, **2006**, 6: 789–802. <https://doi.org/10.1038/nrc1977>
- [66] Smith, N. F., Figg, W. D., Sparreboom, A. Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicology in Vitro*, **2006**, 20: 163–175. <https://doi.org/10.1016/j.tiv.2005.06.045>
- [67] Wilhelm, S. M., Dumas, J., Adnane, L., et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *International Journal of Cancer*, **2011**, 129: 245–255. <https://doi.org/10.1002/ijc.25864>
- [68] Grothey, A., Cutsem, E. V., Sobrero, A., et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *The Lancet*, **2013**, 381: 303–312. [https://doi.org/10.1016/S0140-6736\(12\)61900-X](https://doi.org/10.1016/S0140-6736(12)61900-X)
- [69] Tlemsani, C., Huillard, O., Arrondeau, J., et al. Effect of glucuronidation on transport and tissue accumulation of tyrosine kinase inhibitors: consequences for the clinical management of sorafenib and regorafenib. *Expert Opinion on Drug Metabolism & Toxicology*, **2015**, 11: 785–794. <https://doi.org/10.1517/17425255.2015.1030392>
- [70] Panchal, N. K., Prince Sabina, E. Non-steroidal anti-inflammatory drugs (NSAIDs): a current insight into its molecular mechanism eliciting organ toxicities. *Food and Chemical Toxicology*, **2023**, 172: 113598. <https://doi.org/10.1016/j.fct.2022.113598>
- [71] Bacchi, S., Palumbo, P., Sponta, A., et al. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, **2012**, 11: 52–64. <https://doi.org/10.2174/187152312803476255>
- [72] Bindu, S., Mazumder, S., Bandyopadhyay, U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochemical Pharmacology*, **2020**, 180: 114147. <https://doi.org/10.1016/j.bcp.2020.114147>
- [73] Lazzaroni, M., Bianchi Porro, G. Gastrointestinal side-effects of traditional non-steroidal anti-inflammatory drugs and new formulations. *Alimentary Pharmacology & Therapeutics*, **2004**, 20: 48–58. <https://doi.org/10.1111/j.1365-2036.2004.02037.x>
- [74] Fukumoto, A., Tanaka, S., Shishido, T., et al. Comparison of detectability of small-bowel lesions between capsule endoscopy and double-balloon endoscopy for patients with suspected small-bowel disease. *Gastrointestinal Endoscopy*, **2009**, 69: 857–865. <https://doi.org/10.1016/j.gie.2008.06.007>
- [75] Chan, F. K. L., Hung, L. C. T., Suen, B. Y., et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *New England Journal of Medicine*, **2002**, 347: 2104–2110. <https://doi.org/10.1056/NEJMoa021907>
- [76] Leung, W. K., Bjarnason, I., Wong, V. W., et al. Small bowel enteropathy associated with chronic low-dose aspirin therapy. *The Lancet*, **2007**, 369: 614. [https://doi.org/10.1016/S0140-6736\(07\)60282-7](https://doi.org/10.1016/S0140-6736(07)60282-7)
- [77] Graham, D. Y., Opekun, A. R., Willingham, F. F., et al. Visible small-intestinal mucosal injury in chronic NSAID users. *Clinical Gastroenterology and Hepatology*, **2005**, 3: 55–59. [https://doi.org/10.1016/S1542-3565\(04\)00603-2](https://doi.org/10.1016/S1542-3565(04)00603-2)
- [78] Higuchi, K., Umegaki, E., Watanabe, T., et al. Present status and strategy of NSAIDs-induced small bowel injury. *Journal of Gastroenterology*, **2009**, 44: 879–888. <https://doi.org/10.1007/s00535-009-0102-2>
- [79] Nelson, A. D., Camilleri, M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. *Therapeutic Advances in Gastroenterology*, **2015**, 8: 206–220. <https://doi.org/10.1177/1756283X15578608>
- [80] Zeeh, J., Inglin, R., Baumann, G., et al. Mycophenolate mofetil impairs healing of left-sided colon anastomoses. *Transplantation*, **2001**, 71: 1429. <https://doi.org/10.1097/00007890-200105270-00013>
- [81] Staatz, C. E., Tett, S. E. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Archives of Toxicology*, **2014**, 88: 1351–1389. <https://doi.org/10.1007/s00204-014-1247-1>
- [82] Lévesque, E., Delage, R., Benoit-Biancamano, M. O., et al. The impact of UGT1A8, UGT1A9, and UGT2B7 genetic polymorphisms on the pharmacokinetic profile of mycophenolic acid after a single oral dose in healthy volunteers. *Clinical Pharmacology & Therapeutics*, **2007**, 81: 392–400. <https://doi.org/10.1038/sj.clpt.6100073>
- [83] Staatz, C. E., Tett, S. E. Clinical pharmacokinetics and pharmacodynamics of in solid organ transplant recipients. *Clinical Pharmacokinetics*, **2007**, 46: 13–58. <https://doi.org/10.2165/00003088-200746010-00002>
- [84] Taylor, M. R., Flannigan, K. L., Rahim, H., et al. Vancomycin relieves mycophenolate mofetil-induced gastrointestinal toxicity by eliminating gut bacterial β -glucuronidase activity. *Science Advances*, **2019**, 5: eaax2358. <https://doi.org/10.1126/sciadv.aax2358>

- [85] Corujo-Santana, C., Falcón-González, J. C., Borkoski-Barreiro, S. A., et al. Relación entre hiperbilirrubinemia neonatal e hipoacusia neurosensorial. *Acta Otorrinolaringológica Española*, **2015**, 66: 326–331. <https://doi.org/10.1016/j.otorri.2014.10.001>
- [86] O'Brien, L., Hosick, P. A., John, K., et al. Biliverdin reductase isozymes in metabolism. *Trends Endocrinol Metab*, **2015**, 26: 212–220. <https://doi.org/10.1016/j.tem.2015.02.001>
- [87] Edwinston, A. L., Yang, L., Peters, S., et al. Gut microbial β -glucuronidases regulate host luminal proteases and are depleted in irritable bowel syndrome. *Nature Microbiology*, **2022**, 7: 680–694. <https://doi.org/10.1038/s41564-022-01103-1>
- [88] Vitek, L. Bilirubin as a signaling molecule. *Medicinal Research Reviews*, **2020**, 40: 1335–1351. <https://doi.org/10.1002/med.21660>
- [89] Sundararaghavan, V. L., Sindhwani, P., Hinds Jr, T. D. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas? *Oncotarget*, **2016**, 8: 3640–3648. <https://doi.org/10.18632/oncotarget.12277>
- [90] Bočkor, L., Bortolussi, G., Vodret, S., et al. Modulation of bilirubin neurotoxicity by the abcb1 transporter in the Ugt1-/- lethal mouse model of neonatal hyperbilirubinemia. *Human Molecular Genetics*, **2017**, 26: 145–157. <https://doi.org/10.1093/hmg/ddw375>
- [91] Ho, Y. C., Ho, L. H. C., Ho, K. J. Human hepatic β -glucuronidase: an enzyme kinetic study. *Enzyme*, **2017**, 33: 9–17. <https://doi.org/10.1159/000469398>
- [92] Yang, X. T., Wang, J., Jiang, Y. H., et al. Insight into the mechanism of gallstone disease by proteomic and metaproteomic characterization of human bile. *Frontiers in Microbiology*, **2023**, 14: 1276951. <https://doi.org/10.3389/fmicb.2023.1276951>
- [93] Ho, K. J., Hsu, S. C., Chen, J. S., et al. Human biliary β -glucuronidase: correlation of its activity with deconjugation of bilirubin in the bile. *European Journal of Clinical Investigation*, **1986**, 16: 361–367. <https://doi.org/10.1111/j.1365-2362.1986.tb01010.x>
- [94] Wang, P., Jia, Y., Wu, R., et al. Human gut bacterial β -glucuronidase inhibition: an emerging approach to manage medication therapy. *Biochemical Pharmacology*, **2021**, 190: 114566. <https://doi.org/10.1016/j.bcp.2021.114566>
- [95] Samavat, H., Kurzer, M. S. Estrogen metabolism and breast cancer. *Cancer Letters*, **2015**, 356: 231–243. <https://doi.org/10.1016/j.canlet.2014.04.018>
- [96] Kumari, N., Kumari, R., Dua, A., et al. From gut to hormones: unraveling the role of gut microbiota in (phyto)estrogen modulation in health and disease. *Molecular Nutrition & Food Research*, **2024**, 68: 2300688. <https://doi.org/10.1002/mnfr.202300688>
- [97] Singh, V., Mahra, K., Jung, D., et al. Gut microbes in polycystic ovary syndrome and associated comorbidities: type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and the potential of microbial therapeutics. *Probiotics and Antimicrobial Proteins*, **2024**, 16: 1744–1761. <https://doi.org/10.1007/s12602-024-10262-y>
- [98] Bucurica, S., Lupanciu, M., Ionita Radu, F., et al. Estrobolome and hepatocellular adenomas—connecting the dots of the gut microbial β -glucuronidase pathway as a metabolic link. *International Journal of Molecular Sciences*, **2023**, 24: 16034. <https://doi.org/10.3390/ijms242216034>
- [99] Kwon, Y. H., Khan, W. I. Peripheral serotonin: cultivating companionship with gut microbiota in intestinal homeostasis. *American Journal of Physiology Cell Physiology*, **2022**, 323: C550–C555. <https://doi.org/10.1152/ajpcell.00433.2021>
- [100] Jain, A., Samyukt, A., Jackson, C., et al. Curcumin inhibits PhIP induced cytotoxicity in breast epithelial cells through multiple molecular targets. *Cancer Letters*, **2015**, 365: 122–131. <https://doi.org/10.1016/j.canlet.2015.05.017>
- [101] Zaoui, M., Louadj, L., Ferrand, N., et al. Carcinogenic effect of low doses of polycyclic and heterocyclic aromatic hydrocarbons and amines and lack of protection by inulin supplementation. *Food and Chemical Toxicology*, **2024**, 185: 114454. <https://doi.org/10.1016/j.fct.2024.114454>
- [102] Kaderlik, K. R., Mulder, G. J., Turesky, R. J., et al. Glucuronidation of N-hydroxy heterocyclic amines by human and rat liver microsomes. *Carcinogenesis*, **1994**, 15: 1695–1701. <https://doi.org/10.1093/carcin/15.8.1695>
- [103] Cai, T., Yao, L., Turesky, R. J. Bioactivation of heterocyclic aromatic amines by UDP glucuronosyltransferases. *Chemical Research in Toxicology*, **2016**, 29: 879–891. <https://doi.org/10.1021/acs.chemrestox.6b00046>
- [104] Tang, Y., LeMaster, D. M., Nauwelaers, G., et al. UDP-glucuronosyltransferase-mediated metabolic activation of the tobacco carcinogen 2-Amino-9H-Pyrido[2,3-b]Indole*. *Journal of Biological Chemistry*, **2012**, 287: 14960–14972. <https://doi.org/10.1074/jbc.M111.320093>
- [105] Kemper, L., Hensel, A. *Campylobacter jejuni*: targeting host cells, adhesion, invasion, and survival. *Applied Microbiology and Biotechnology*, **2023**, 107: 2725–2754. <https://doi.org/10.1007/s00253-023-12456-w>
- [106] Ahmad Mansour, N., Loubet, P., Pouget, C., et al. Staphylococcus aureus toxins: an update on their pathogenic properties and potential treatments. *Toxins (Basel)*, **2021**, 13: 677. <https://doi.org/10.3390/toxins13100677>
- [107] Platt Samoraj, A. Toxigenic properties of yersinia enterocolitica biotype 1a. *Toxins (Basel)*, **2022**, 14: 118. <https://doi.org/10.3390/toxins14020118>
- [108] Olsen, S. J., Ying, M., Davis, M. F., et al. Multidrug-resistant salmonella typhimurium infection from milk contaminated after pasteurization. *Emerging Infectious Diseases*, **2004**, 10: 932–935. <https://doi.org/10.3201/eid1005.030484>
- [109] Sun, H., Wang, M., Liu, Y., et al. Regulation of flagellar motility and biosynthesis in enterohemorrhagic Escherichia coli O157:H7. *Gut Microbes*, **2022**, 14: 2110822. <https://doi.org/10.1080/19490976.2022.2110822>
- [110] Josephs Spaulding, J., Beeler, E., Singh, O. V. Human microbiome versus food-borne pathogens: friend or foe. *Applied Microbiology and Biotechnology*, **2016**, 100: 4845–4863. <https://doi.org/10.1007/s00253-016-7523-7>
- [111] Threlfall, E. J., Ward, L. R., Frost, J. A., et al. The emergence and spread of antibiotic resistance in food-borne bacteria. *International Journal of Food Microbiology*, **2000**, 62: 1–5. [https://doi.org/10.1016/S0168-1605\(00\)00351-2](https://doi.org/10.1016/S0168-1605(00)00351-2)
- [112] Meng, J., Abu, Y. F., Zhang, Y., et al. Opioid-induced microbial dysbiosis disrupts irinotecan (CPT-11) metabolism and increases gastrointestinal toxicity in a murine model. *British Journal of Pharmacology*, **2023**, 180: 1362–1378. <https://doi.org/10.1111/bph.16020>
- [113] Domellof, L., Darby, L., Hanson, D., et al. Fecal sterols and bacterial beta-glucuronidase activity: a preliminary metabolic epidemiology study of healthy volunteers from Umea, Sweden, and metropolitan New York. *Nutrition and Cancer*, **1982**, 4: 120–127. <https://doi.org/10.1080/01635588209513747>
- [114] McIntosh, F. M., Maison, N., Holtrop, G., et al. Phylogenetic distribution of genes encoding β -glucuronidase activity in human colonic bacteria and the impact of diet on faecal glycosidase activities. *Environmental Microbiology*, **2012**, 14: 1876–1887. <https://doi.org/10.1111/j.1462-2920.2012.02711.x>
- [115] Reddy, B. S., Engle, A., Simi, B., et al. Effect of dietary fiber on colonic bacterial enzymes and bile acids in relation to colon cancer. *Gastroenterology*, **1992**, 102: 1475–1482. [https://doi.org/10.1016/0016-5085\(92\)91704-8](https://doi.org/10.1016/0016-5085(92)91704-8)
- [116] Verma, A., Shukla, G. Administration of prebiotic inulin suppresses 1,2 dimethylhydrazine dihydrochloride induced procarcinogenic biomarkers fecal enzymes and preneoplastic lesions in early colon carcinogenesis in sprague dawley rats. *Journal of Functional Foods*, **2013**, 5: 991–996. <https://doi.org/10.1016/j.jff.2013.02.006>
- [117] Geier, M. S., Butler, R. N., Howarth, G. S. Probiotics, Prebiotics and synbiotics: a role in chemoprevention for colorectal cancer? *Cancer Biology & Therapy*, **2006**, 5: 1265–1269. <https://doi.org/10.4161/cbt.5.10.3296>

- [118] Madhu, A. N., Prapulla, S. G. *In vitro* fermentation of prebiotics by *Lactobacillus plantarum* CFR 2194: selectivity, viability and effect of metabolites on β -glucuronidase activity. *World Journal of Microbiology & Biotechnology*, **2012**, 28: 901–908. <https://doi.org/10.1007/s11274-011-0887-z>
- [119] Mahdy, M. S., Azmy, A. F., Dishisha, T., et al. Irinotecan-gut microbiota interactions and the capability of probiotics to mitigate irinotecan-associated toxicity. *BMC Microbiology*, **2023**, 23: 53. <https://doi.org/10.1186/s12866-023-02791-3>
- [120] Maseda, D., Ricciotti, E. NSAID-gut microbiota interactions. *Frontiers in Pharmacology*, **2020**, 11: 1153. <https://doi.org/10.3389/fphar.2020.01153>
- [121] Elmassry, M. M., Kim, S., Busby, B. Predicting drug-metagenome interactions: variation in the microbial β -glucuronidase level in the human gut metagenomes. *PLOS One*, **2021**, 16: e0244876. <https://doi.org/10.1371/journal.pone.0244876>
- [122] Walsh, J., Olavarria Ramirez, L., Lach, G., et al. Impact of host and environmental factors on β -glucuronidase enzymatic activity: implications for gastrointestinal serotonin. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **2020**. <https://doi.org/10.1152/ajpgi.00026.2020>
- [123] Kim, D. H., Jin, Y. H. Intestinal bacterial β -glucuronidase activity of patients with colon cancer. *Archives of Pharmacological Research*, **2001**, 24: 564–567. <https://doi.org/10.1007/BF02975166>
- [124] Lin, H. Y., Chen, C. Y., Lin, T. C., et al. Entropy-driven binding of gut bacterial β -glucuronidase inhibitors ameliorates irinotecan-induced toxicity. *Communications Biology*, **2021**, 4: 280. <https://doi.org/10.1038/s42003-021-01815-w>
- [125] Lietzan, A. D., Simpson, J. B., Walton, W. G., et al. Microbial β -glucuronidases drive human periodontal disease etiology. *Science Advances*, **2023**, 9: 3390. <https://doi.org/10.1126/sciadv.adg3390>
- [126] Zhang, L. T., Westblade, L. F., Iqbal, F., et al. Gut microbiota profiles and fecal beta-glucuronidase activity in kidney transplant recipients with and without post-transplant diarrhea. *Clinical Transplantation*, **2021**, 35: e14260. <https://doi.org/10.1111/ctr.14260>
- [127] Cheng, K. W., Tseng, C. H., Chen, I. J., et al. Inhibition of gut microbial β -glucuronidase effectively prevents carcinogen-induced microbial dysbiosis and intestinal tumorigenesis. *Pharmacological Research*, **2022**, 177: 106115. <https://doi.org/10.1016/j.phrs.2022.106115>
- [128] Letertre, M. P. M., Bhatt A. P., Harvey, M., et al. Characterizing the metabolic effects of the selective inhibition of gut microbial β -glucuronidases in mice. *Scientific Reports*, **2022**, 12: 17435. <https://doi.org/10.1038/s41598-022-21518-4>
- [129] Tian, X. G., Yan, J. K., Sun, C. P., et al. Amentoflavone from *Selaginella tamariscina* as a potent inhibitor of gut bacterial β -glucuronidase: inhibition kinetics and molecular dynamics stimulation. *Chemico-Biological Interactions*, **2021**, 340: 109453. <https://doi.org/10.1016/j.cbi.2021.109453>
- [130] Bai, Y., Chen, L., Wang, P. P., et al. Discovery of a naturally occurring broad-spectrum inhibitor against gut bacterial β -glucuronidases from *Ginkgo biloba*. *Food & Function*, **2021**, 12: 11190–11201. <https://doi.org/10.1039/D1FO01748A>
- [131] Wang, P., Wu, R., Jia, Y., et al. Inhibition and structure-activity relationship of dietary flavones against three loop 1-type human gut microbial β -glucuronidases. *International Journal of Biological Macromolecules*, **2022**, 220: 1532–1544. <https://doi.org/10.1016/j.ijbiomac.2022.09.018>
- [132] Han, Y., Liu, Y. T., Chen, L., et al. Hinokiflavone from *Platycladus acutemarginatus* as a potent broad-spectrum inhibitor of gut microbial loop-1 β -glucuronidases: inhibition kinetics and molecular simulation. *Chemico-Biological Interactions*, **2024**, 404: 111261. <https://doi.org/10.1016/j.cbi.2024.111261>
- [133] Weng, Z. M., Wang, P., Ge, G. B., et al. Structure-activity relationships of flavonoids as natural inhibitors against *E. Coli* β -glucuronidase. *Food and Chemical Toxicology*, **2017**, 109: 975–983. <https://doi.org/10.1016/j.fct.2017.03.042>
- [134] Lin, C. H., Chou, H. J., Chang, C. C., et al. Chemical constituent of β -glucuronidase inhibitors from the root of *Neolitsea acuminatissima*. *Molecules*, **2020**, 25: 5170. <https://doi.org/10.3390/molecules25215170>
- [135] Yue, B., Gao, R., Lv, C., et al. Berberine improves irinotecan-induced intestinal mucositis without impairing the anti-colorectal cancer efficacy of irinotecan by inhibiting bacterial β -glucuronidase. *Frontiers in Pharmacology*, **2021**, 12: 774560. <https://doi.org/10.3389/fphar.2021.774560>
- [136] Kamel, E. M., Alkhayl, F. F. A., Alqhtani, H. A., et al. Dissecting molecular mechanisms underlying the inhibition of β -glucuronidase by alkaloids from *Hibiscus trionum*: integrating in vitro and in silico perspectives. *Computers in Biology and Medicine*, **2024**, 180: 108969. <https://doi.org/10.1016/j.combiomed.2024.108969>
- [137] Higashi, R., Ohta, E., Omura, H., et al. Triterpenoid saponins from the fruits of *Symplocos lucida* as β -glucuronidase inhibitors. *Chemistry & Biodiversity*, **2022**, 19: e202200774. <https://doi.org/10.1002/cbdv.202200774>
- [138] Yu, H. F., Cheng, Y. C., Wu, C. M., et al. Diverse diterpenoids with α -glucosidase and β -glucuronidase inhibitory activities from *Euphorbia milii*. *Phytochemistry*, **2022**, 196: 113106. <https://doi.org/10.1016/j.phytochem.2022.113106>
- [139] Higashi, R., Ohta, E., Nehira, T., et al. Acylated secoiridoid glucosides isolated from the fruit extract of *Symplocos lucida* inhibit β -glucuronidase. *Phytochemistry Letters*, **2022**, 51: 127–131. <https://doi.org/10.1016/j.phytol.2022.08.008>
- [140] Khan, K. M., Saad, S. M., Shaikh, N. N., et al. Synthesis and β -glucuronidase inhibitory activity of 2-arylquinazolin-4(3h)-ones. *Bioorganic & Medicinal Chemistry*, **2014**, 22: 3449–3454. <https://doi.org/10.1016/j.bmc.2014.04.039>
- [141] Taha, M., Sultan, S., Nuzar, H. A., et al. Synthesis and biological evaluation of novel *N*-arylidenequinoline-3-carbohydrazides as potent β -glucuronidase inhibitors. *Bioorganic & Medicinal Chemistry*, **2016**, 24: 3696–3704. <https://doi.org/10.1016/j.bmc.2016.06.008>
- [142] Zhou, T. S., Wei, B., He, M., et al. Thiazolidin-2-cyanamides derivatives as novel potent *Escherichia coli* β -glucuronidase inhibitors and their structure-inhibitory activity relationships. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2020**, 35: 1736–1742. <https://doi.org/10.1080/14756366.2020.1816998>
- [143] Li, Y. S., He, M., Zhou, T. S., et al. 2,5-Disubstituted furan derivatives containing 1,3,4-thiadiazole moiety as potent α -glucosidase and *E. Coli* β -glucuronidase inhibitors. *European Journal of Medicinal Chemistry*, **2021**, 216: 113322. <https://doi.org/10.1016/j.ejmech.2021.113322>
- [144] Graboski, A. L., Simpson, J. B., Pellock, S. J., et al. Advanced piperazine-containing inhibitors target microbial β -glucuronidases linked to gut toxicity. *RSC Chemical Biology*, **2024**, 5: 853–865. <https://doi.org/10.1039/D4CB00058G>
- [145] Yang, W., Wei, B., Yan, R. Amoxapine demonstrates incomplete inhibition of β -glucuronidase activity from human gut microbiota. *SLAS Discovery*, **2018**, 23: 76–83. <https://doi.org/10.1177/2472555217725264>
- [146] Zhong, Z., Sun, B., Shu, N., et al. Ciprofloxacin blocked enterohepatic circulation of diclofenac and alleviated NSAID-induced enteropathy in rats partly by inhibiting intestinal β -glucuronidase activity. *Acta Pharmacologica Sinica*, **2016**, 37: 1002–1012. <https://doi.org/10.1038/aps.2016.54>
- [147] Li, P., Zhang, R., Zhou, J., et al. Vancomycin relieves tacrolimus-induced hyperglycemia by eliminating gut bacterial β -glucuronidase enzyme activity. *Gut Microbes*, **2024**, 16: 2310277. <https://doi.org/10.1080/19490976.2024.2310277>
- [148] Maier, L., Goemans, C. V., Wirbel, J., et al. Unravelling the collateral damage of antibiotics on gut bacteria. *Nature*, **2021**, 599: 120–124. <https://doi.org/10.1038/s41586-021-03986-2>
- [149] Farzia, Rehman, S., Ikram, M., et al. Synthesis, characterization, hirshfeld surface analysis, antioxidant and selective β -glucuronidase inhibitory studies of transition metal complexes of

- hydrazide based schiff base ligand. *Scientific Reports*, **2024**, 14: 515. <https://doi.org/10.1038/s41598-023-49893-6>
- [150] Cheng, K. W., Tseng, C. H., Yang, C. N., et al. Specific inhibition of bacterial β -glucuronidase by pyrazolo[4,3-c]quinoline derivatives via a pH-dependent manner to suppress chemotherapy-induced intestinal toxicity. *Journal of Medicinal Chemistry*, **2017**, 60: 9222–9238. <https://doi.org/10.1021/acs.jmedchem.7b00963>
- [151] Salar, U., Khan, K. M., Syed, S., et al. Synthesis, *in vitro* β -glucuronidase inhibitory activity and *in silico* studies of novel (*E*)-4-Aryl-2-(2-(pyren-1-ylmethylene)hydrazinyl)thiazoles. *Bioorganic Chemistry*, **2017**, 70: 199–209. <https://doi.org/10.1016/j.bioorg.2016.12.011>
- [152] Salar, U., Taha, M., Ismail, N. H., et al. Thiadiazole derivatives as new class of β -glucuronidase inhibitors. *Bioorganic & Medicinal Chemistry*, **2016**, 24: 1909–1918. <https://doi.org/10.1016/j.bmc.2016.03.020>
- [153] Iraj, A., Nouri, A., Edraki, N., et al. One-pot synthesis of thioxotetrahydropyrimidine derivatives as potent β -glucuronidase inhibitor, biological evaluation, molecular docking and molecular dynamics studies. *Bioorganic & Medicinal Chemistry*, **2020**, 28: 115359. <https://doi.org/10.1016/j.bmc.2020.115359>
- [154] Taha, M., Ullah, H., Al Muqarrabun, L. M. R., et al. Synthesis of bis-indolylmethanes as new potential inhibitors of β -glucuronidase and their molecular docking studies. *European Journal of Medicinal Chemistry*, **2018**, 143: 1757–1767. <https://doi.org/10.1016/j.ejmech.2017.10.071>
- [155] Awolade, P., Cele, N., Kerru, N., et al. Therapeutic significance of β -glucuronidase activity and its inhibitors: a review. *European Journal of Medicinal Chemistry*, **2020**, 187: 111921. <https://doi.org/10.1016/j.ejmech.2019.111921>
- [156] Baharudin, M. S., Taha, M., Imran, S., et al. Synthesis of indole analogs as potent β -glucuronidase inhibitors. *Bioorganic Chemistry*, **2017**, 72: 323–332. <https://doi.org/10.1016/j.bioorg.2017.05.005>
- [157] Pellock, S. J., Creekmore, B. C., Walton, W. G., et al. Gut microbial β -glucuronidase inhibition via catalytic cycle interception. *ACS Central Science*, **2018**, 4: 868–879. <https://doi.org/10.1021/acscentsci.8b00239>
- [158] Taha, M., Ismail, N. H., Imran, S., et al. Synthesis of novel disulfide and sulfone hybrid scaffolds as potent β -glucuronidase inhibitor. *Bioorganic Chemistry*, **2016**, 68: 15–22. <https://doi.org/10.1016/j.bioorg.2016.07.002>
- [159] Xu, K., Ying, L., Ying, T., et al. Design, synthesis, and biological evaluation of (thio)urea derivatives as potent *Escherichia coli* β -glucuronidase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2024**, 39: 2387415. <https://doi.org/10.1080/14756366.2024.2387415>
- [160] Nguyen, M. K., Nguyen, V. P., Yang, S. Y., et al. Astraeleanosides e-p, oleanane-type triterpenoid saponins from the aerial parts of *Astragalus membranaceus bunge* and their β -glucuronidase inhibitory activity. *Bioorganic Chemistry*, **2024**, 145: 107230. <https://doi.org/10.1016/j.bioorg.2024.107230>
- [161] Li, X. N., Hua, L. X., Zhou, T. S., et al. Cinnamic acid derivatives: inhibitory activity against *Escherichia coli* β -glucuronidase and structure-activity relationships. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2020**, 35: 1372–1378. <https://doi.org/10.1080/14756366.2020.1780225>
- [162] Sun, C. P., Yan, J. K., Yi, J., et al. The study of inhibitory effect of natural flavonoids toward β -glucuronidase and interaction of flavonoids with β -glucuronidase. *International Journal of Biological Macromolecules*, **2020**, 143: 349–358. <https://doi.org/10.1016/j.ijbiomac.2019.12.057>
- [163] Fotschki, B., Juśkiewicz, J., Jurgoński, A., et al. Grinding levels of raspberry pomace affect intestinal microbial activity, lipid and glucose metabolism in wistar rats. *Food Research International*, **2019**, 120: 399–406. <https://doi.org/10.1016/j.foodres.2019.03.014>
- [164] Rao, G., Yu, H., Zhang, M., et al. α -Glucosidase and bacterial β -glucuronidase inhibitors from the stems of *Schisandra sphaerandra* staph. *Pharmaceuticals (Basel)*, **2022**, 15: 329. <https://doi.org/10.3390/ph15030329>
- [165] Kim, D. H., Shim, S. B., Kim, N. J., et al. β -Glucuronidase-Inhibitory activity and hepatoprotective effect of *Ganoderma lucidum*. *Biological & Pharmaceutical Bulletin*, **1999**, 22: 162–164. <https://doi.org/10.1248/bpb.22.162>
- [166] Yang, S. Y., Phong, N. V. Phenolic compounds from the stems of *Zanthoxylum piperitum* and their inhibition of β -glucuronidase: enzyme kinetics, molecular docking, and molecular dynamics analysis. *Journal of Molecular Structure*, **2024**, 1317: 139117. <https://doi.org/10.1016/j.molstruc.2024.139117>
- [167] Gao, R., Yue, B., Lv, C., et al. Targeted inhibition of *Gus*-expressing *Enterococcus faecalis* to promote intestinal stem cell and epithelial renovation contributes to the relief of irinotecan chemotoxicity by dehydrodiisoeugenol. *Acta Pharmaceutica Sinica B*, **2024**, 14: 5286–5304. <https://doi.org/10.1016/j.apsb.2024.09.018>
- [168] Lee, H. W., Choo, M. K., Bae, E. A., et al. β -Glucuronidase inhibitor tectorigenin isolated from the flower of *Pueraria thunbergiana* protects carbon tetrachloride-induced liver injury. *Liver International*, **2003**, 23: 221–226. <https://doi.org/10.1034/j.1600-0676.2003.00830.x>
- [169] Shim, S. B., Kim, N. J., Kim, D. H. β -Glucuronidase inhibitory activity and hepatoprotective effect of 18 β -glycyrrhethinic acid from the rhizomes of *Glycyrrhiza uralensis*. *Planta Medica*, **2000**, 66: 40–43. <https://doi.org/10.1055/s-2000-11109>
- [170] Wei, B., Yang, W., Yan, Z. X., et al. Prenylflavonoids sanggenon c and kuwanon g from mulberry (*Morus alba* L.) as potent broad-spectrum bacterial β -glucuronidase inhibitors: biological evaluation and molecular docking studies. *Journal of Functional Foods*, **2018**, 48: 210–219. <https://doi.org/10.1016/j.jff.2018.07.013>
- [171] Challa, A. P., Hu, X., Zhang, Y. Q., et al. Virtual screening for the discovery of microbiome β -glucuronidase inhibitors to alleviate cancer drug toxicity. *Journal of Chemical Information and Modeling*, **2022**, 62: 1783–1793. <https://doi.org/10.1021/acs.jcim.1c01414>
- [172] Wu, L., Jiang, J., Jin, Y., et al. Activity-based probes for functional interrogation of retaining β -glucuronidases. *Nature Chemical Biology*, **2017**, 13: 867–873. <https://doi.org/10.1038/nchembio.2395>