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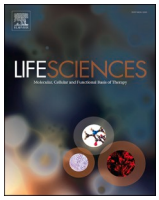

Drug enteric metabolism in gut microbiota-brain crosstalk

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ABSTRACT

Neurodegenerative diseases (NDs), such as Alzheimer's (AD) and Parkinson's disease (PD) represent the leading cause of illness and disability worldwide. In the effort to unveiling the etiopathogenesis of these neurological diseases, increasing attention has recently been paid to the emerging role of the gut microbiota (GMB) in the so-called gut-brain axis, and to the correlation of neurodegenerative processes with intestinal dysbiosis, either of genetic bases or induced by drugs and their metabolites. Over time, there has been a notable surge in the quantity of scientific publications pertaining to the gut-brain axis and GMB metabolism, reaching top levels in 2023–2025. As a result, the body of research on the effects of the gut-brain axis on AD and PD has begun to increase. Nonetheless, the identification of gut-derived metabolites and their effects on the central nervous system (CNS) is frequently missing or only partially reported. It is therefore necessary to raise awareness on the importance of enteric metabolism and its assessment while designing new drugs and investigating their pharmacokinetic properties, since both healthy and dysbiotic gut can hamper or modify drugs activity and efficacy. This review aims at providing a critical overview of gut-derived metabolism of different drugs, focusing on their effects on the GMB and gut-brain axis. The discussion focused on common therapeutic agents against AD and PD, as well as non-prescription drugs and food supplements with known beneficial effects on the CNS, reviewing relevant literature of the last decade.

1. Introduction

Upon administration, the fate of drugs mainly depends on their metabolism in the various compartments of the human body. Although drug catabolism may occur via several routes, metabolic modifications can generate bioactive substances, starting either from masked prodrugs or actual medications. Numerous enzymes and biochemical reactions account for these activation/inactivation events, thus influencing stability, bioavailability, and excretion of drugs. When it comes to the metabolic pathways of xenobiotics, it is well known that liver represents the primary site responsible for both Phase I and Phase II metabolism of most species [1]. In addition to the liver, several other organs contribute to the biotransformation of drugs, affecting their half-life, plasma concentration, and efficacy. Indeed, kidneys and lungs are significantly

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contributing to the metabolism and excretion of drugs, especially after processes of glucuronidation or after administration via the inhalatory route [2,3]. Locally, skin also contributes to the transformations of topical medications [4]. Increasing attention has been paid over the years to the effect of the gastrointestinal tract on drugs metabolism. The gut microbiota (GMB) and the microbiome composition are now considered as "fingerprints" of an individual and these unique features contribute to the wide efficacy variability of drugs in different subjects. This variability is especially evident in complex diseases such as neurodegenerative diseases (NDs), where the gut-brain axis serves as a critical communication network linking the gastrointestinal tract and central nervous system (CNS) [5]. Within this framework, Parkinson's disease (PD) and Alzheimer's disease (AD) emerge as paradigmatic conditions. These two NDs are the most prevalent in the general population, but their pathophysiological mechanisms underscore a profound interplay between GMB, systemic inflammation, and neuronal health, as well as between GMB and response to symptomatic therapy. The relevance of these diseases is heightened by their socioeconomic burden and the pressing need for novel therapeutic avenues to target both motor and cognitive dysfunction, impacting on the natural history of neurodegeneration [6]. PD and AD share intriguing parallels in their relationship with the GMB, which plays a critical role in AD and PD pathogenesis. In fact, gut dysbiosis has been linked to early motor and non-motor symptoms in PD patients, including gastrointestinal dysfunction, which often precedes motor manifestations by years [7]. Similarly, in AD, alterations in the GMB are associated with systemic inflammation, increased permeability of the blood-brain barrier (BBB), and amyloid-beta (Aβ) aggregation [8]. While many of these findings are correlative, experimental studies provide stronger evidence of a causative contribution: for instance, transplantation of the GMB from PD or AD patients into germ-free or antibiotic-treated mice can recapitulate motor deficits, cognitive decline, and enhanced Aβ pathology [9–12]. These observations support the view that the GMB is not merely a passive player but an active modulator of disease onset and progression.

In support of this claim, a search on the PubMed database, using 4 keywords combinations, which are "gut+microbiota+metabolism", "gut-brain+axis", "gut-brain+Alzheimer", and "gut-brain+Parkinson", has been performed and the results are reported in Fig. 1.1A–B. As a matter of fact, the number of scientific publications related to the gut-brain axis activity (blue bars, Fig. 1.1A) and the GMB metabolism (orange bars, Fig. 1.1A) has significantly increased over the years, reaching a top level in 2023–2025. Accordingly, also the reported literature dealing with the effects of the gut-brain axis on AD and PD (green and purple bars, respectively, Fig. 1.1B) has started to raise, being almost absent in 2015 but significantly populating the database in the last five years. Although the trend in this last search is slightly less consistent, by plotting the results of the four searches all together, as in Fig. 1.2, a constant trend and an important increase in the number of scientific publications on this subject can be appreciated.

This review aims at discussing the effect of the GMB in generating drugs metabolites, and the impact of these metabolites on microbiota dysbiosis and gut-brain axis. Our purpose is to raise awareness among researchers about considering enteric metabolism as one of the key factors in the pharmacokinetic of new drugs. In addition, the modification induced by gut on drugs commonly used against NDs can influence their efficacy and the progression of the disease. But at the same time, the dysbiosis frequently observed in patients affected by AD and PD may correlate to a different outcome in the metabolic fate of prescribed drugs. Accordingly, we reviewed all available information of GMB metabolism on anti-NDs drugs, including the interesting case of levodopa (LD), the main drug to treat PD. We also decided to consider different classes of non-prescription drugs and food supplements with known beneficial effects in NDs. After careful evaluation, we focused our attention on acetyl-L-carnitine, rifaximin, statins and the non-steroidal anti-inflammatory drug (NSAID) diclofenac. All these drugs have been reported to have an impact on the GMB, either by inducing neuroprotection and modulating inflammatory processes, but little is known on whether these GMB effects interfere with their potential neuroprotective actions.

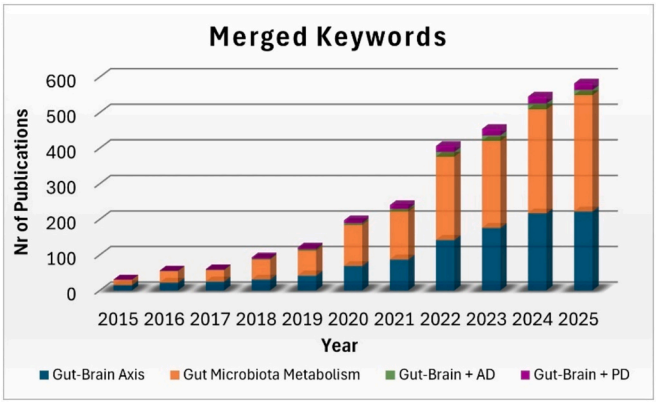


Fig. 1.2. Plotting of the number of scientific publications (excluding review papers) retrieved in the PubMed database using the 4 reported keywords in the last decade (2015–2025).

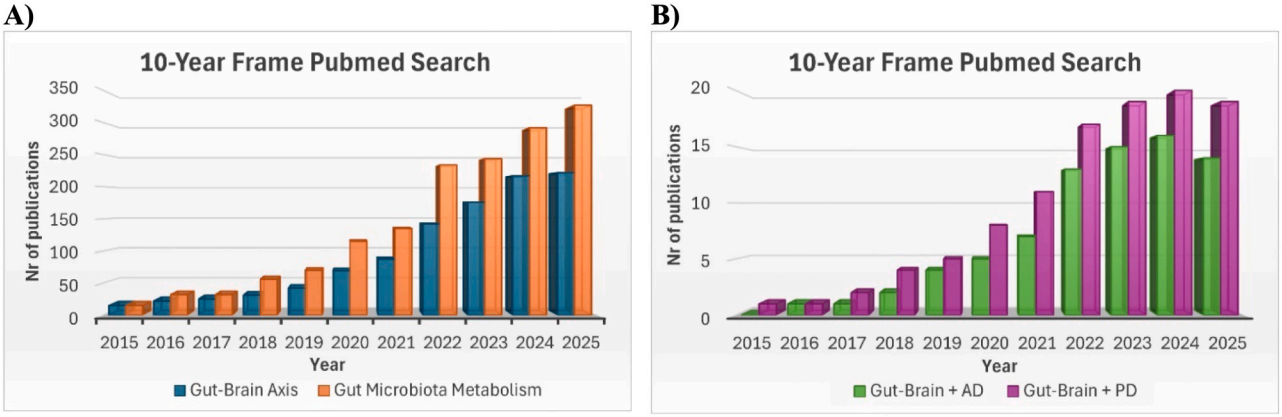


Fig. 1.1. A) Number of scientific publications (excluding review papers) retrieved in the PubMed database using "gut+brain+axis" and "gut+microbiota+metabolism" keywords combinations in the last decade (2015–2025). B) Number of scientific publications (excluding review papers) retrieved in the PubMed database using gut+brain+Alzheimer" and "gut+brain+Parkinson" keywords combinations in the last decade (2015–2025).

2. GMB and enteric drugs metabolism

2.1. Background, composition and physiological roles of the GMB

The GMB is primarily composed of bacteria, but it also includes archaea, fungi, protozoa, and viruses. Trillions of microorganisms, specifically 10^{13}–10^{14} bacteria belonging to approximately a thousand different species, can be identified in the gut of healthy humans. The composition of the microbiota is dynamic and constantly changes in response to diet, environmental conditions, individual lifestyle, age, and drug intake, among other factors. The GMB (principally bacteria) colonizing the human intestinal tract is a complex microbial consortium that begins developing before birth, evolves throughout life, and plays a crucial role in the host's health. It constantly interacts with its host and significantly influences several physiological functions [13]. The GMB symbiotically interacts with the host and may depend on host metabolism to obtain the energy needed for its own sustenance, but it can also release molecules that the host can use as energy sources. These include short-chain fatty acids (SCFAs), used as energy source by the colonic epithelium in the form of butyrate, vitamins and amino acids or that can be used to build up energy such as secondary bile acids, caseinolytic protease and lipopolysaccharide, that can specifically activate signalling pathways in the host [14], thus affecting food intake, gut motility, nutrient absorption and energy consumption and intake [15,16]. The host-GMB interaction also contributes to the maturation of the immune and the endocrine systems since birth; intestinal commensals can secrete host hormones, influence the human host through them and be influenced by them, too [17]. Since the GMB communication with the host is multifaceted and spans from the metabolic, endocrine, humoral, immunological and neural pathways, the GMB is now considered a vital organ [18].

2.2. The role of GMB in drugs metabolism

Every part of the human body (e.g. skin, airways, urogenital tract, gastrointestinal tract and mouth) has a specific microbiome composition, which is profoundly linked to its function and physicochemical characteristics. Human genomes are 99.9 % similar, but gut microbiomes, the ensemble of all the genetic information of the microorganisms living in the intestine, can be less than 10 % similar between two individuals. Consequently, numerous studies have focused on uncovering the diversity of the microbe-encoded enzymes and the mechanisms that govern their drug metabolism capacity. Moreover, the GMB has been the most studied microbial environment in the human body in terms of drug response, partly because it harbours by far the largest microbial biomass in the body and thus possesses the major microbial potential for drug metabolism, and partly because stool, which represents a good sampling method for the large intestine luminal content, is easy to collect. Recently, research on the intestinal mucous-associated microbiome (MAM), which is distinct from the luminal microbiome, has gained more attention due to the importance of these microbes in immune and metabolic health. In fact, microbes that live in this district have a direct connection with the intestinal barrier function due to their proximity to the epithelium. Moreover, their alterations are associated with Crohn's disease, irritable bowel syndrome (IBS) and colorectal cancer [19]. The study of this niche though is hindered by the necessity of using invasive procedures to obtain this microbiota, with possible disruption of the lumen and consequent impairment of the concomitant study of both the lumen and the MAM ecosystems; thus, the studies on this ecosystem are very limited. Swallowable bacteria-sampling capsules could be a painless and trustworthy alternative to biopsies, lavages and brushing of the intestinal epithelia [20] and are under development.

As a matter of fact, the GMB has the potential to alter the metabolic outcome of drugs, toxic substances, and heavy metals (xenobiotics), thus modifying their pharmacokinetics. Xenobiotics can be then chemically modified in the intestinal tract directly upon administration or after reaching the intestine via enterohepatic recirculation. The modifications can lead to an increased metabolism of the molecules or their bioactivation, depending on the interactions that can happen with the available microbial species. The microbiome can also reduce the xenobiotic absorption by direct sequestration of the molecules or by limiting their intake by reinforcing the mucous layer and cell-cell adhesion of intestinal epithelial cells; moreover, human gene expression can be regulated by the microbiota. On the other hand, xenobiotics may interfere with all these processes disrupting the microbiota composition and metabolism.

2.3. The gut-brain axis

The gut-brain axis (and brain-gut axis) refers to the bidirectional communication network between the gastrointestinal tract, including the enteric nervous system (ENS) and the CNS, which encompasses the hypothalamic–pituitary–adrenal axis. This connection involves neural, hormonal, and immunological pathways and plays a crucial role in maintaining homeostasis, as well as influencing gut health, brain function, and overall well-being. For example, SCFAs like acetate, propionate, and butyrate are byproducts of bacterial fermentation of complex plant-based polysaccharides in the intestine. They can cross the BBB, supporting gut-brain communication and barrier integrity [21]. Moreover, neurotransmitters and metabolites produced by the GMB work as chemical signals influencing the gut-brain axis, but also the immune system, the neuroendocrine system, and the vagus nerve [22]. Among the neurotransmitters produced or influenced by GMB activity we can list γ-aminobutyric acid [23,24], dopamine [25], and serotonin [26,27] (Fig. 2.1), with the synthesis of latter also influenced by the GMB via the regulation of tryptophan intake [28,29]. Additionally, specific species of bacteria can dangerously convert LD, a medication used to treat PD, to dopamine in the gut, resulting in decreased neuronal uptake and dopamine production in the CNS [30].

2.4. Leaky gut and leaky brain

The concepts of leaky gut and leaky brain illustrate the deep interconnection between gut health and brain function, emphasizing the critical role of the gut-brain axis. By the late 2000s, it was evident that disruptions to the gut barrier could destabilize homeostasis and drive systemic inflammation. The GMB, as an integral part of the gut-brain neuroendocrine metabolic axis, plays a pivotal role in maintaining this balance [32]. Leaky gut occurs when the intestinal barrier becomes overly permeable, allowing harmful substances, such as toxins, bacteria, and undigested food particles, to pass into the bloodstream. This triggers systemic inflammation and immune responses, potentially leading to autoimmune diseases, food sensitivities, and chronic illnesses. Similarly, the phenomenon of leaky brain refers to a compromised BBB, a critical protective structure that regulates the entry of substances into the brain. Strikingly, the integrity of both the intestinal lining and the BBB depends on shared molecular mechanisms, particularly the function of tight junction (TJ) proteins. These proteins regulate barrier permeability, and their disruption (whether due to inflammation, oxidative stress, or external factors) can compromise both barriers simultaneously, revealing a shared vulnerability [5]. Beyond epithelial and endothelial cells, the nervous system plays an essential role in barrier regulation. In the CNS, astrocytes are crucial for the formation and maintenance of the BBB by modulating endothelial TJs and providing trophic and metabolic support [33]. In the gut, enteric glial cells exert analogous functions, and their ablation disrupts intestinal barrier integrity, while their release of mediators such as *S*-nitrosoglutathione promotes TJ protein expression and epithelial protection [34]. Other studies further extended this concept, showing that enteric glial cells are central regulators of epithelial barrier function and immunomodulation, suggesting striking parallels between astrocytes and enteric glial cells [35,36]. These data reinforce the idea that the gut–brain axis is not only an

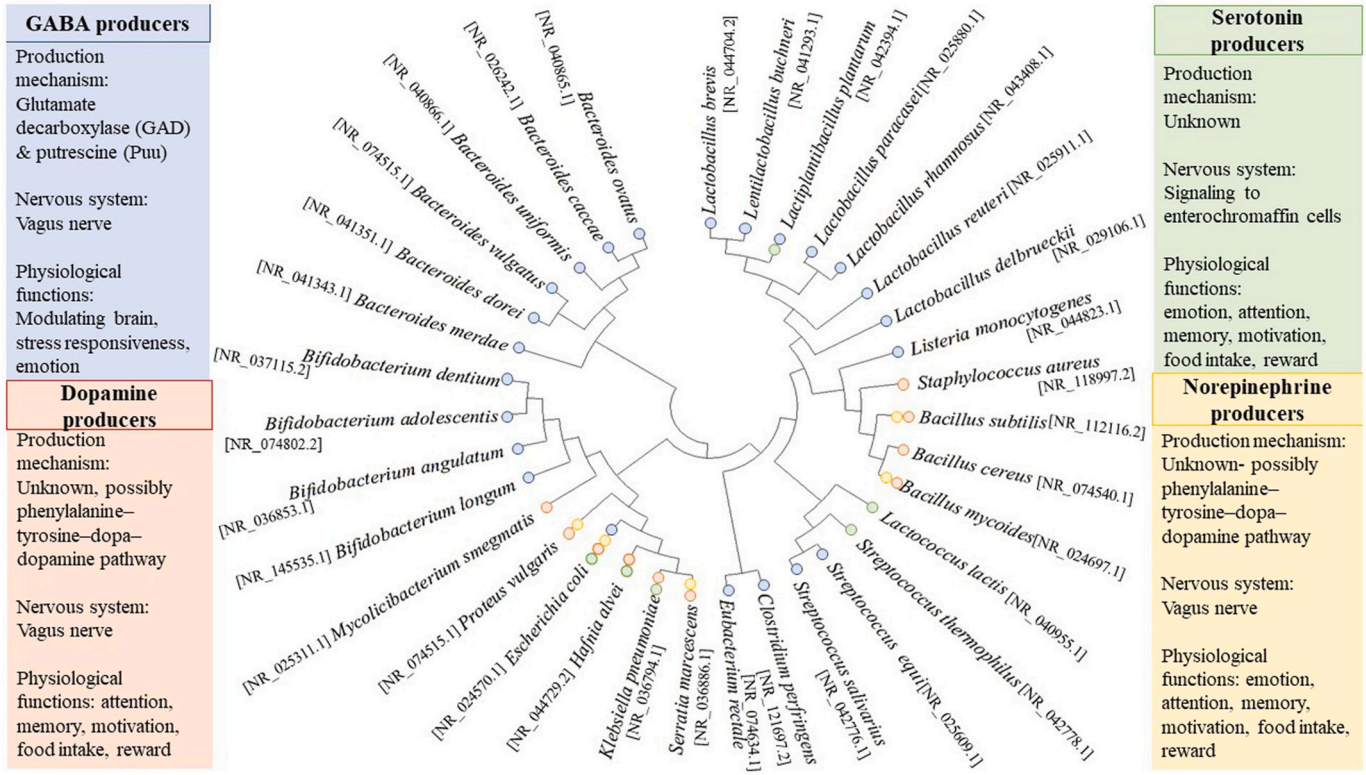


Fig. 2.1. Bacteria involved in neurotransmitters modulation are indicated at the centre of the figure and divided into four categories, indicated in the left and right panels in violet (GABA producers), orange (dopamine producers), green (serotonin producers) and yellow (norepinephrine producers) [31].

immunoendocrine but also a neuroglial network linking barrier integrity and systemic homeostasis. When gut integrity is compromised, systemic inflammation and altered signalling can directly affect brain health, increasing the risk of neurological complications. Certain medications, such as NSAIDs, antibiotics, and proton pump inhibitors, can exacerbate these vulnerabilities. By disrupting the GMB, damaging the intestinal lining, or altering mucus production, these drugs can increase intestinal permeability and potentially compromise brain health through the interconnected gut-brain axis. This intricate relationship underscores the importance of preserving the integrity of both the gut and the BBB. Supporting gut health is not only essential for preventing systemic inflammation and chronic illnesses but also for safeguarding neurological well-being and overall health [37].

3. The GMB in NDs

3.1. Mechanisms of interaction between GMB and NDs

Across conditions such as PD and AD, patients often exhibit reduced overall microbial diversity and a notable loss of key SCFA-producing taxa, like *Faecalibacterium* and *Roseburia* [38,39]. Concurrently, there is an enrichment of pro-inflammatory microbes, including certain *Proteobacteria*, which can compromise gut barrier integrity and potentially intensify systemic and neuroinflammatory processes [40]. These alterations are mechanistically linked to increased gut permeability (leaky gut), heightened peripheral inflammation, and changes in immune signalling that can traverse the BBB, thereby exacerbating pathological protein aggregation and neuronal damage [41]. In fact, emerging evidence suggests that this heightened inflammatory milieu may accelerate processes like protein misfolding, facilitating the aggregation of α-synuclein in PD [40,42] or Aβ in AD [43,44]. Overall, these patterns suggest a prominent role for microbiome-driven inflammation and metabolic dysregulation in the pathophysiology of NDs, independently from pharmacological interventions. These alterations can compromise gut epithelial integrity, allowing bacterial products (e.g., lipopolysaccharide) to reach the systemic circulation, drive immune activation, and exacerbate neuroinflammation. Altogether, these findings highlight a critical role for GMB in mediating NDs mechanisms (independent of medication influences) through pathways involving inflammation, metabolic dysfunction, and the potential modulation of pathological protein aggregation.

3.2. The effect of PD and AD therapies on the GMB

GMB dysbiosis could result not only from chronic and neurodegenerative processes but may also come from the action of drugs on the microbiota. Some treatments, including antibiotics, can modify GMB thus reducing inflammation and protecting the BBB, potentially improving motor and cognitive functions in PD [45]. Other GMB changes, such as increased propionate production, have been linked to neuroprotective effects, potentially ameliorating motor deficits in PD [46]. However, a significant and multifaceted effect on GMB is also reported for different medications used in the management of PD and AD (Fig. 3.1). These latter can alter the composition and function of GMB, which in turn can influence the efficacy and side effects of the treatments.

LD and dopamine agonists (e.g. pramipexole, ropinirole) can lead to changes in GMB composition, such as increased *Lactobacillus* and *Bifidobacterium*, and decreased *Lachnospiraceae* and *Prevotellaceae* [47]. These changes can contribute to the gastrointestinal dysfunctions commonly seen in PD patients. In fact, it is documented how pharmacological treatments for PD are associated with increased gastrointestinal issues, such as constipation, due to altered GMB [47] and reduced butyrate production [48], which ultimately affects the ENS [49]. PD medications can also reduce small intestinal motility and lead to bacterial overgrowth, further complicating gastrointestinal symptoms [47]. Melis and co-workers studied the impact of LD on GMB alterations through the effects of LD and LD-carbidopa intestinal gel (LCIG) on 107

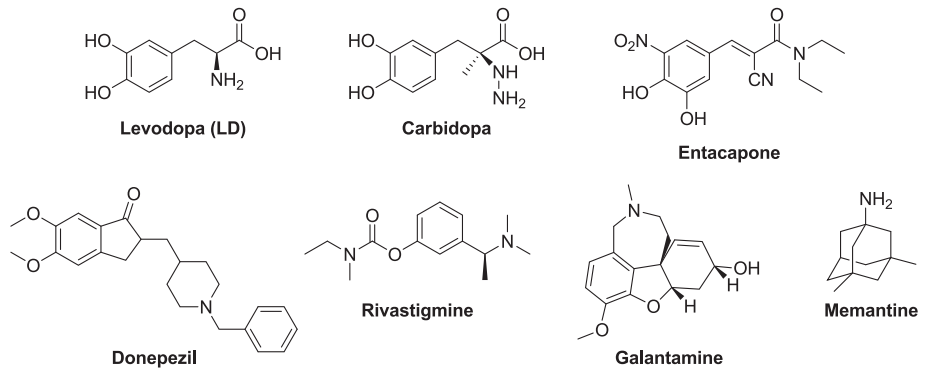


Fig. 3.1. Structures of representative drugs commonly used against PD (LD, carbidopa, and entacapone) and AD (donepezil, rivastigmine, galantamine and memantine) which have been investigated for their role in modulating GMB activity.

PD patients [50]. Results showed a reduction of *Blautia* and *Lachnospirae* genus in the LD group, while in the LCIG group increased *Enterobacteriaceae*, *Escherichia*, and *Serratia* bacteria, evidencing significant alterations of the GMB after the treatment. Similar studies by Palacios and collaborators did not observe significant changes in the composition of the GMB of PD patients [51], but certain *Lactobacillus* species resulted increased during the treatment, potentially affecting LD bioavailability [47]. PD therapies based on LD usually rely on drugs cocktails which include inhibitors of LD metabolism. This is the case of carbidopa, an inhibitor of LD decarboxylation, and entacapone, which inhibits the catechol-*O*-methyltransferase (COMT), a magnesium-dependent enzyme responsible the *O*-methylation and inactivation of LD [52]. Recent studies show that entacapone affects the phylogenetic composition of the GMB in PD patients [53]. While it doesn't affect bacteria diversity or species richness, Entacapone increases *Actinobacteria* abundance and decreases *Firmicutes*, potentially due to iron sequestration, as reported by Pereira and colleagues [54]. This leads to reduced activity of key microbiota members like *Bacteroides*, *Ruminococcus*, and *Clostridium* species. Additionally, changes in amino acids metabolism, such as alanine, aspartate, and glutamate, are linked to common side effects of entacapone, including auditory hallucinations and fatigue [53]. Unfortunately, the specific effects on GMB of several other drugs (including tolcapone, opicapone, safinamide, benserazide, etc.) in PD patients are not directly addressed in the available data. However, the impact on colonic motility through increased dopamine suggests a potential influence on gut function [55,56].

Donepezil, an acetylcholinesterase inhibitor used to treat mild to severe cognitive symptoms in AD, showed a considerable effect on GMB in an in vivo model of AD. The faecal microbial community of mice after Aβ injection differed from those injected with Aβ and donepezil, these latter showing higher levels of *Verrucomicrobia* and relative richness in *Blautia* and *Akkermansia* taxa [57]. The abundance of such taxa displayed a positive influence on the disease progression, being associated to important AD risk factors like obesity and insulin resistance [58]. Changes in superoxide dismutase activity have also been reported, thus impacting on oxidative stress [59]. Donepezil treated animals also had higher levels of oxalate, glycerol, xylose, and palmitoleate in faeces and oxalate, pyroglutamic acid, hypoxanthine, and inosine in brain tissues, suggesting a positive influence on AD-induced cognitive dysfunction via the gut-brain axis. Studies involving rivastigmine and galantamine suggested that these drugs did not directly affect GMB viability but may influence intestinal functions [60]. Similarly, memantine was reported to positively affect GMB in AD, particularly when combined with probiotics like *L. plantarum* [61].

4. The effect of GMB on drugs: the case of levodopa

It is evident that the administration of different drugs, including those prescribed against NDs, frequently induces changes in the composition and activity of GMB. These changes have been reported in both healthy subject and PD or AD patients, in which the gut flora has already been compromised by the disease itself. Interestingly, knowing the effect of a healthy or altered GMB on drugs is essential to discuss the possible lack of efficacy or unexpected side effects linked to gut-derived metabolites. Recent literature highlighted the effects of GMB on LD, which still represents the first line treatment in PD. LD enters the brain, and it is converted to dopamine by the aromatic amino acid decarboxylase enzyme. However, the decarboxylation reaction may also occur in peripheral areas, including the gastrointestinal tract, and more than 50 % of LD fails to reach the brain. Hence, free dopamine generated in the periphery causes a plethora of heterogeneous side-effects. Maini Rekdal and co-workers identified in 2019 a bacteria strain possibly responsible for gut-induced decarboxylation of LD, reducing its availability and efficacy [62]. They found a conserved tyrosine decarboxylase (TDC) enzyme in *Enterococcus faecalis* that can metabolize LD, as part of an interspecies pathway also involving *Eggerthella lenta* bacteria, responsible for the gut metabolism of the drug. The bacterial TDC is a pyridoxal phosphate (PLP)–dependent enzyme, able to simultaneously decarboxylate both LD and tyrosine (its preferred substate). The dopamine resulting from TDC activity can undergo further metabolism which has been linked to a single-nucleotide polymorphism (SNP) of a molybdenum cofactor–dependent dopamine dehydroxylase (Dadh) enzyme (Fig. 4.1). Accordingly, the abundance of *Enterococcus faecalis*, TDC, and the individual SNPs of Dadh are associated with LD and dopamine metabolism in the complex GMB environment of PD patients. Therefore, variations in the expression or activity of these species have been associated with heterogenic efficacy and harmful side effects of LD. Similarly, van Kessel et al. investigated the activity of LD metabolizing gut bacteria, particularly in the jejunum, where the drug is primarily absorbed. They concluded that TDC genes, present in the genome of *Lactobacillus* and *Enterococcus* bacteria species, encoded for a TDC enzyme that efficiently converted LD to dopamine, thus influencing its in situ levels. They also found a clear correlation between the relative abundance of TDC-expressing bacteria with the need for higher doses of LD and the drug plasma concentration [63]. Therefore, at fixed doses of LD, GMB activity could be responsible for the lack of efficacy and for the increased side-effects caused by the drug treatment. In line with this, piperine, a natural alkaloid found in black pepper, has been suggested as an adjuvant in PD treatment due to its ability to suppress TDC activity and increase dopamine availability [64], as demonstrated by Hu and colleagues in a 6-hydroxydopamine-lesioned rats model. Analogously, bacteriophages against *Enterococcus faecalis* proved to be efficacious in eliminating bacterial TDC gene copies and transcripts, hampering the conversion of LD to dopamine in the gastrointestinal tract [65]. A similar effect was obtained with a derivative of the natural compound honokiol (HNK), a lignan named Mito-*ortho*-HNK isolated from the trees of the genus Magnolia. This acts as a mitochondria-targeted compound and suppresses the growth of *Enterococcus faecalis*, decreasing dopamine

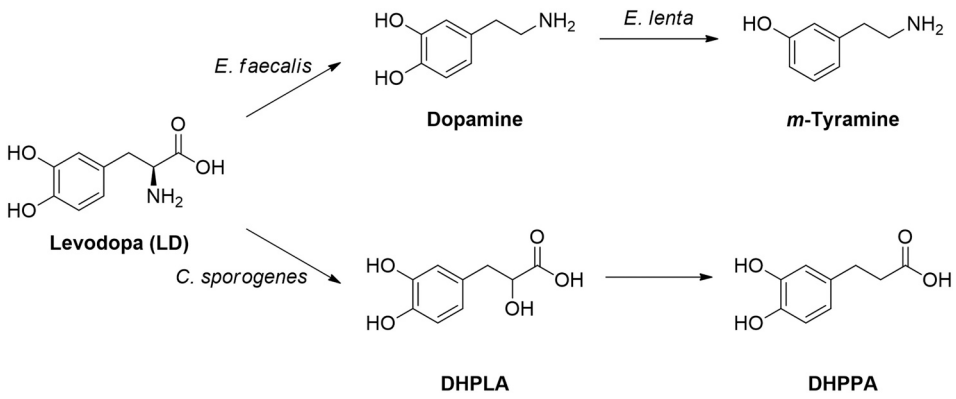


Fig. 4.1. The metabolism of LD by gut bacteria. *E. faecalis* and *E. lenta* account for the majority of gut metabolism. *C. sporogenes* is responsible for additional derivatization and loss of active L-DOPA. DHPLA = 3-(3,4-dihydroxyphenyl) lactic acid; DHPPA = 3-(3,4-dihydroxyphenyl) propionic acid.

levels in the gut while increasing LD availability in the brain [30]. In addition to *Enterococcus fecaelis, Enterococcus faecium,* and *Eggerthella lenta* [62,63], also *Helicobacter pylori* [66–68] and *Clostridium sporogenes* [69] can affect the metabolism and absorption of LD [70]. *Helicobacter pylori* effect might be correlated to its ability to delay gastric emptying, resulting in delayed LD entry and transport in the duodenum [67]. *Clostridium sporogenes* contributes to deaminate proteinogenic aromatic amino acids through an anaerobic deamination pathway. It has been demonstrated that LD can undergo the same metabolic pathway, leading to the production of 3-(3,4-dihydroxyphenyl)lactic acid (DHPLA, Fig. 4.1), which is then converted to 3-(3,4-dihydroxyphenyl) propionic acid (DHPPA, Fig. 4.1), ultimately causing reduced ileal motility in ex vivo studies [69]. LD represents a perfect example of a drug whose fate is affected by GMB, contributing to reinforce the interest around the effect that gut metabolism has on the efficacy of drugs commonly used against chronic disorders. A similar information is lacking for other ND drugs, such as donepezil in AD, which is still limited to the effect of the drug on the GMB, but additional studies are now more than ever necessary to unveil unknown pharmacokinetic mechanisms.

5. Influence of GMB on agents with potential neuroprotective effects

Due to the increasing interest on the role of GMB on drugs efficacy and metabolism, we decided to collect additional information on the gut-derived metabolites of different classes of frequently used drugs or food supplements. Based on data collected in preclinical studies or evidence from mostly non-randomized, uncontrolled human studies, or case-series, the following compounds, endowed with known potential beneficial effects in neurodegenerative conditions, have been selected and discussed:

i) *Acetyl-L-Carnitine (ALC)*, one of the most common food supplements principally involved in fats and energy metabolism, frequently studied for its beneficial effects against dementia and cognitive disorders [71].
ii) *Rifaximin (RX)*, as the representative of the antibiotic class of drugs, which mainly exerts its activity at the gut level because of its low or absent systemic bioavailability. Both preclinical and clinical studies have recently highlighted its contribution to NDs (such as PD) and neuroinflammation [45].
iii) *Simvastatin (SV) and other statins*, which are the first-choice treatment for dyslipidaemia and have been already investigated for their neuroprotective role [72,73].
iv) *Diclofenac (DCF)*, as representative analogue of the NSAIDs, which is also one of the most used drugs for relieving painful statuses associated to rheumatoid arthritis and related disorders. It has been also indicated as a possible co-adjuvant in the treatment of PD and AD [74].

At variance from already reported literature, we herein focus on the chemical features of gut-derived metabolites for the above-mentioned drugs, to allow considerations on the structure-activity relationships (SARs) of these metabolites (summarized in Table 1 at the end of this section). The information collected also includes microbiological and clinical aspects connected to the use of these drugs.

5.1. Acetyl-L-carnitine (ALC)

L-Carnitine (LC) is an endogenous quaternary ammonium compound, biosynthesized from the amino acid L-lysine, crucially involved in energy metabolism and in the catabolism of fatty acids [75]. It possesses antioxidant properties, regulates brain neurotransmitters such as acetylcholine, serotonin, and dopamine, and influences neurotrophic factors (e.g. neuronal grow factor) and metabotropic glutamate receptors through epigenetic mechanisms [76]. LC is converted in vivo to the corresponding acetylated product, ALC, which is transported from the mitochondrial matrix to the cytosol where it promotes enzymatic glucose oxidation in carbohydrates metabolism [77].

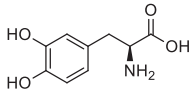
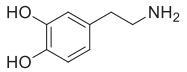
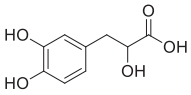
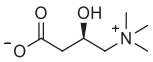
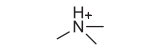
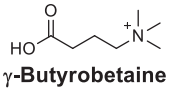
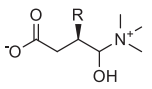
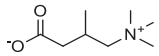
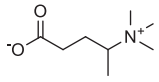
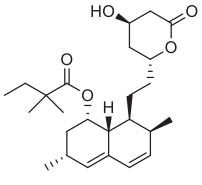
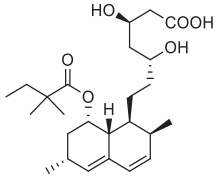
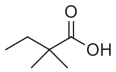
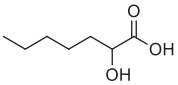
The dietary consumption of ALC is reported to have beneficial effects in patients affected by mild to severe cognitive impairment, including AD [78,79], as well as its use as a food supplement [80]. Several studies highlighted neuroprotective [81], neurotrophic [82], antidepressive, and analgesic effects of ALC [83], either in in vitro or in vivo models. Four randomized controlled trials (RCTs) [84–87] showed that ALC improved specific aspects of cognitive and behavioural function in patients with senile cognitive impairment or mild-to-moderate AD, including verbal ability and selective attention. Preclinical studies conducted on animal models of PD (e.g., induced by 6-hydroxydopamine or rotenone) [88,89] suggested that ALC can mitigate oxidative stress, reduce inflammation, restore mitochondrial function, and promote neurogenesis and neuronal survival. Moreover, administration of ALC to valproate-exposed rats (as an autism model) alleviated behavioural abnormalities and ameliorated GMB-derived SCFAs, intestinal barrier and recovery of microglia and brain inflammation [90]. Nonetheless, there is still an open debate around the potential application for these supplements in neurodegeneration [71].

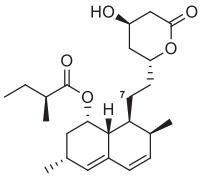
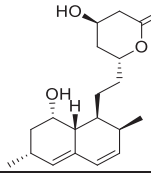
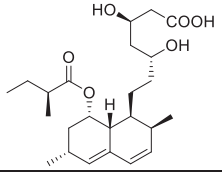
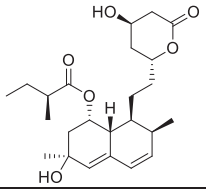
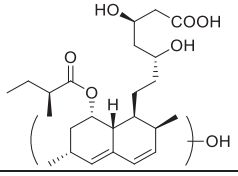
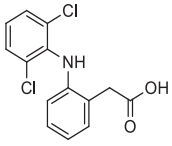
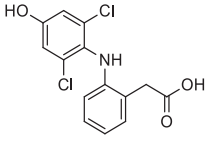
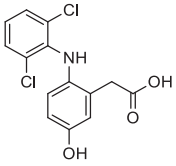
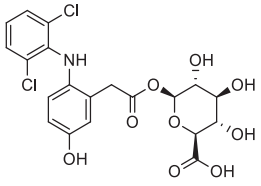
Similarly to phosphatidylcholine and choline, LC is generally found in meats, in particular red meat, and dairy foods such as milk-derived products, peanut butter, and asparagus [91]. When ingested, LC undergoes GMB metabolism with the consequent release of trimethylamine (TMA), later converted into trimethylamine-*N*-oxide (TMAO) by oxidative metabolism in the liver. However, GMB action on LC is a more complex process which encompasses aerobic and anaerobic bacterial metabolic pathways, also leading to the formation of γ-butyrobetaine

(γ-BB) and other oxidized products, ultimately producing TMA and TMAO (Fig. 5.1).

For example, *Acinetobacter calcoaceticus* can degrade LC into TMA and malic acid (used as a source of carbon) by cleaving the carbon-nitrogen bond [92]. A similar mechanism has been observed in bacteria belonging to the *Enterobacteriaceae* family such as *Serratia marcescens* [93] and others like *Escherichia coli*, *Salmonella typhimurium*, *Proteus vulgaris* and *Proteus mirabilis*, that can convert LC into γ-BB via crotonobetaine reductase [94]. In anaerobic conditions, when oxygen or other common electron acceptors are unavailable, LC and crotonobetaine can be used as final electron acceptors [95]. Therefore, LC can be catabolized by gut bacteria to be used as nitrogen and/or carbon source, or electron acceptor and osmolyte, thus affecting GMB composition. The O_2-indipendent metabolism has been recently re-investigated to unveil the mechanism beyond the production of TMA from LC in the anoxic human gut. The anaerobic metabolism of γ-BB is only found in selected

Table 1
Summary of the structures of gut-derived metabolites reported in the literature for the drugs of interest. If known, bacteria or enzymes involved in the metabolic process have been listed.

Drug	Target	Metabolite	Bacteria[a], enzymes[b] or type of metabolism[c] involved
 Levodopa (LD)	Dopamine agonist (anti-PD drug)	 Dopamine	*E. faecalis*[a] (Ref. 62) *L. brevis*[a] (Ref. 63)
		 DHPLA	*C. sporogenes*[a] (Ref. 69)
 L-Carnitine	Food supplement	 Trimethylamine	*A. calcoaceticus* (Ref. 92)
		 γ-Butyrobetaine	- S. *marcescens*[a] - *E. coli*[a] - *S. typhimurium*[a] - *P. vulgaris*[a] - *P. mirabilis*[a] (Ref. 95)
		R = H, OH 	*Aerobic metabolism*[c] (Ref. 96)
		 3M-4-TMAB	- *C. clostridioforme*[a] - *C. symbiosum*[a] (Ref. 98)
		 4-TMAP	
 Simvastatin	Anti-hyperlipidemic drug	 Simvastatin acid	*Hydrolytic metabolism*[c] (Ref. 117-118)
		 2,2-Dimethylbutanoic acid	
		 2-Hydroxyheptanoic acid	

Drug	Target	Metabolite	Bacteria[a], enzymes[b] or type of metabolism[c] involved
 Lovastatin	Anti-hyperlipidemic drug		*Hydrolytic metabolism*[c] (Ref. 119)
			
			*Oxidative metabolism*[c] (Ref. 119)
			*Hydrolytic and oxidative metabolism*[c] (Ref. 119)
 Diclofenac	NSAID (Phenylacetic acid)	 4'-Hydroxydiclofenac	*Oxidative metabolism*[c] (Ref. 130)
		 5-Hydroxydiclofenac	
		 Diclofenac *O*-acyl glucuronide	- *UGT2B17*[b] (Ref. 131) - *Bacterial* β-*glucuronidase*[b] (Ref. 132)

[a]Bacteria involved in the generation of metabolites; [b]Enzymes involved in the generation of metabolites; [c]Type of metabolic pathway; DHPLA: 3-(3,4-dihydroxyphenyl) lactic acid; 3M-4-TMAB: 3-methyl-4-(trimethylammonio)butanoate; 4-TMAP: 4-(trimethylammonio)pentanoate.

groups of bacteria and evidence suggests that this pathway might be associated with pathological states [96]. In addition, it has been reported that the ingestion of high doses of LC modifies mice GMB, leading to alterations in the richness of gut bacteria [97]. Anaerobic commensal bacteria from the *Lachnospiraceae* family (*C. clostridioforme* and *C. symbiosum*) have been identified as responsible for the formation of other LC derivatives, such as 3-methyl-4-(trimethylammonio)butanoate (3M-4-TMAB) and 4-(trimethylammonio)pentanoate (4-TMAP) [98]. These compounds further generate alterations of the GMB and metabolic dysfunctions, ultimately worsening the negative effects of gut-induced LC metabolism.

5.2. Rifaximin (RX)

RX is a semi-synthetic non-aminoglycoside antibiotic belonging to the family of rifamycins, a subclass of the larger family of ansamycins (Fig. 5.2). Its mechanism of action encompasses the inhibition of bacterial RNA synthesis by binding to the β-subunit of the DNA-dependent RNA polymerase of Gram-positive and Gram-negative anaerobic and aerobic bacteria [99]. RX possesses low absorption in the gastrointestinal tract, therefore it acts as a non-systemic agent principally used to treat intestinal infections, such as travellers' diarrhoea, or the IBS with diarrhoea [100].

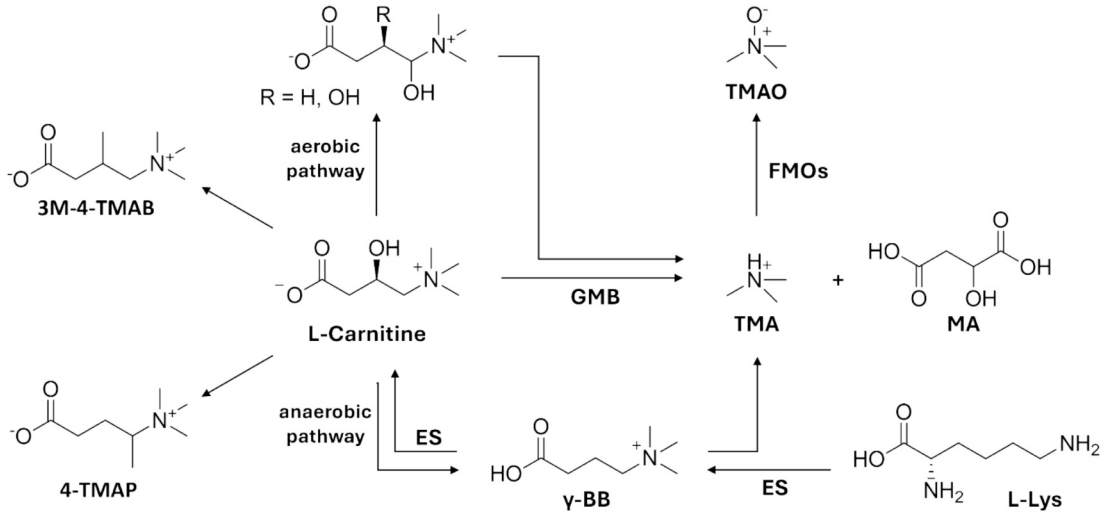


Fig. 5.1. GMB-derived metabolic pathways and liver microsomal activity on L-carnitine (LC). 3M-4-TMAB: 3-methyl-4-(trimethylammonio)butanoate; 4-TMAP: 4-(trimethylammonio)pentanoate; γ-BB: γ-butyrobetaine; ES: endogenous synthesis; FMOs: liver flavin-containing monooxygenase; GMB: gut microbiota; MA: Malic acid; TMA: trimethylamine; TMAO: trimethylamine *N*-oxide; Lys: lysine.

The use of RX as a modulator of GMB displayed positive effects in the presence of NDs such as AD and PD, due to its ability to influence GMB composition and activity. In fact, by changing gut flora and reducing neurotoxic microbial drivers of inflammation, RX could significantly affect cognitive dysfunctions by directly targeting the gut-brain axis. A pilot study by Suhocki et al demonstrated the ability of RX to increase the abundance of beneficial neuroprotective *Firmicutes* strains such as *Lactobacillus*, *Erysipelatoclostridium, Faecalitalea, Erysipelotrichaceae, Anaerostipes, Blautia and Ruminiclostridium*. This was accompanied by significantly lower neurofilament light levels and serum interleukin (IL)-6 levels, proving the hypothesis of a favourable effect mediated by GMB on neurodegeneration without serious adverse events. Although cognitive measures, such as the mini-mental state examination, did not show significant changes, reductions in inflammatory biomarkers suggest potential disease-modifying effects of RX in AD. Moreover, the study highlights the critical link between GMB and systemic inflammation, further supporting the therapeutic relevance of gut-brain axis modulation in neurodegeneration [101]. Similarly, in a transgenic mice PD model, the treatment with RX attenuated serum levels of IL-1, IL-6, and tumour necrosis factor (TNF)-α, thus indicating a reduction of systemic inflammation, possibly contributing to preserve BBB integrity and significantly preserving neuronal viability in the hippocampus. In PD patients, RX increased significantly the relative abundance of the genus *Flavonifractor* after 1-week treatment without eliciting severe side effects [45]. In addition, a randomized, double-blind, placebo-controlled study in healthy subjects, confirmed a modulatory activity of RX on frequency-specific functional connectivity of the insular cortex. These results suggested a potential role of RX as a central mediator of cortical functional brain connectivity alterations, following modifications of GMB, that could involve cognitive flexibility and memory processing [102]. On the gut-brain axis side, this non-absorbable antibiotic can also improve depressive-like behaviour caused by chronic unpredictable mild stress (CUMS) in adolescent rats. This effect was associated with the increase of *Ruminococcus bromii* and *Lachnospiraceae* bacterial families and higher level of butyric acid in the brain [103], as well as to RX influence on hippocampal tryptophan pathway metabolic disorders linked to CUMS [104]. However, further large-scale studies are essential to validate these initial observations and explore the long-term disease-modifying properties of RX in clinical settings.

Although the GMB can be modulated by RX, on the contrary, there is no current evidence showing that the GMB can modify this antibiotic.

5.3. Statins

Statins (Fig. 5.3) have a long history of use in the treatment of cardiovascular diseases because of their ability to control the levels of cholesterol and possibly reduce inflammation.

They act as inhibitors of hydroxymethylglutaryl coenzyme A reductase thus lowering the level of lipoproteins and facilitating the removal of low-density lipoproteins (LDL) from the bloodstream by decreasing the synthesis of cholesterol and increasing the number of LDL receptors in hepatocyte membranes. Therefore, statins are currently the first-choice treatment for hyperlipidaemia [105].

In addition to its antihyperlipidemic effects, statins have also been investigated for their direct neuroprotective properties. Simvastatin (SV) has been tested in an animal model of AD, where it was able to preserve learning and memory functions as a result of a reduction in systemic and neuronal inflammation, inhibition of neurodegeneration

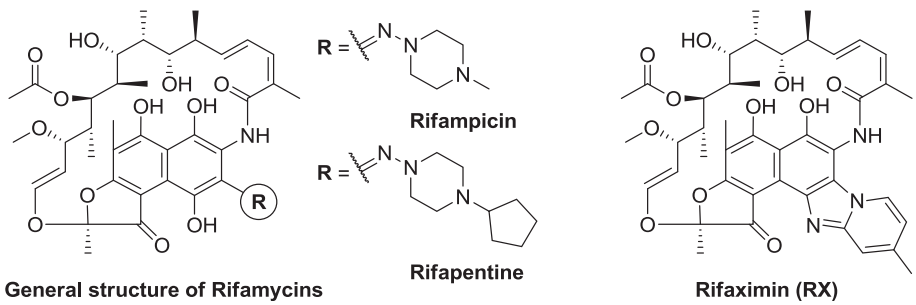


Fig. 5.2. General structure of rifamycins (such as rifampicin and rifapentine) and rifaximin (RX).

and Aβ deposition, and modulation of the gut-brain axis [106]. Specifically, the oral administration of the drug strengthened the TJ between intestinal cells and enhanced the activity of the GMB. Moreover, SV decreased the levels of IL-1β and TNF-α in plasma and in the hippocampus, where a significant reduction in cell death and Aβ plaques was reported. In naturally aging rats, long-term high-doses of atorvastatin (AV) demonstrated improved cognitive-related behavioural scores in three commonly used tests, the Y-maze, the novel recognition object, and the Morris water maze tests. Additionally, the abundance and diversity of intestinal flora was significantly modified, with a higher probiotic flora and a lower *Clostridium perfringens* levels [107]. By modulating the microbial composition and the intestinal barrier function, AV has also been reported to alleviate microglia-mediated neuroinflammation in ischemic stroke mice [108]. Analogously, the treatment with AV and rosuvastatin (RV) in obese mice increased anti-inflammatory bacterial genera like *Bacteroides*, *Butyricimonas*, and *Mucispirillum*, and microbiota transplantation from RV-treated mice ameliorated hyperglycemia in recipient animals [109]. In hypercholesterolemic patients treated with AV, anti-inflammatory bacteria such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Oscillospira* genus were increased, while proinflammatory species like *Desulfovibrio* sp. and bile acid-associated species such as *Bilophila wadsworthia* and *Bifidobacterium bifidum* were found to be decreased by the treatment [110]. Additional support for a potential neuroprotective effect of statins comes from epidemiological studies showing that their use is associated with a reduced risk of dementia and AD, with meta-analyses reporting a 20–32 % lower risk [111]. Although RCTs show limited improvements in cognitive scores, statins may slow neuropsychiatric decline and improve daily living activities. Moreover, lipophilic statins like AV and SV, which cross the BBB, are linked to a 23–58 % lower risk of PD [112,113]. However, RCTs in PD patients provided mixed results, necessitating further investigation into their neuroprotective potential.

All the beneficial effects on NDs were also correlated to an enhanced production of SCFAs, due to the statin-induced changes in GMB composition. An increase of butyrate-producing bacteria, like *F. prausnitzii* and *Butyricimonas*, is suggested to play a major role [114]. In fact, butyrate ameliorates BBB integrity by improving the activity of antioxidant systems and increasing the expression of TJ proteins [115]. Following SV treatment, SCFAs levels were found to be increased in the faeces of rats in an ovariectomized/D-galactose AD animal model, leading to tightens intestinal cell junctions, and to reduce hippocampal Aβ plaques and cell death [106]. For most SCFAs, no systematic investigation on their role in NDs is yet available, although some of them (such as valeric and isovaleric acid) have been shown to regulate

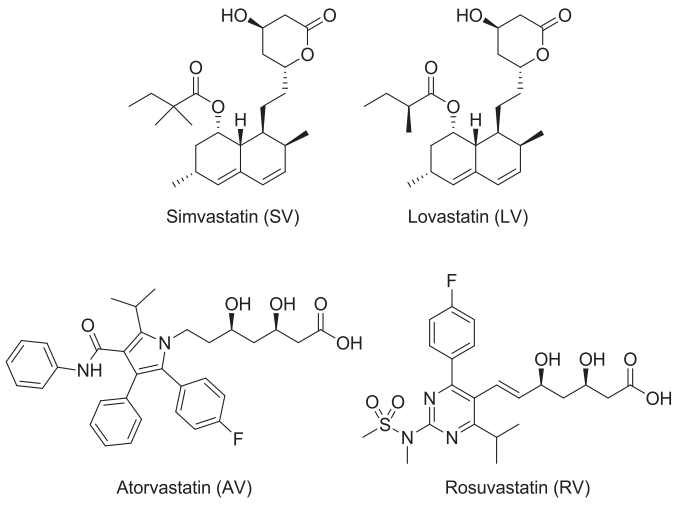


Fig. 5.3. Structure of the most representative statins, namely simvastatin (SV), lovastatin (LV), atorvastatin (AV), and rosuvastatin (RV).

astrocyte and microglia activation, as well as to reduce inflammation and Aβ and tau proteins aggregation in AD models [116].

While GMB role in mediating the neuroprotective effect of statins has received considerable attention, less is known regarding how the GMB influences statins pharmacokinetics. Interestingly, Aura et al in 2010 reported structural information on gut-derived SV metabolites generated in an in vitro model of the colon tract [117]. They demonstrated the formation of SCFAs, including lactic, 2-hydroxyisovaleric and 3-hydroxybutanoic acid, as a result of human faecal microbiota activity (Fig. 5.4). The metabolic processes that mainly affected SV are:

i) the hydrolysis of the ester functionality at position 8, affording 2,2-dimethylbutanoic acid. Additional metabolism of 2,2-dimethylbutanoic acid resulted in the formation of 2-hydroxyisovaleric acid and 3-hydroxybutanoic acid.
ii) the opening of the lactone ring and the C16-C7 bond cleavage with the release of hydroxylated heptanoic acids.
iii) dehydroxylation and cyclisation reactions of 2-hydroxyheptanoic acid to produce heptanoic acid cyclohexanecarboxylic acid.
iv) demethylation reactions of 2-hydroxyheptanoic acid with the formation of shorter homologous acids, possibly leading to the formation of lactic acid as well. However, this latter acid might be also derived from the metabolism of excipients used in the formulation.

Other metabolites have been structurally identified in different tissues in vivo (rats) with the primary SV metabolite, simvastatin acid (SVA), also found in faeces [118]. No harmful effects have been associated with the presence of these metabolites, but it is essential to consider these processes when establishing a pharmacokinetic and pharmacodynamic study.

Lovastatin (LV) has also been the object of a metabolic study using human and rat faecal samples [119]. The incubation of the drug with faecal preparations produced four metabolites (M1–4, Fig. 5.5), indicating a significant involvement of the GMB in LV metabolism. These metabolites structurally correspond to:

i) the demethylbutyryl derivative (M1) obtained via hydrolysis of the ester functionality at position 8.
ii) the active hydroxy acid metabolite (M2), afforded via the ring-opening reaction on the lactone moiety.
iii) the hydroxylated derivative in position 10 (M3).
iv) an additional hydroxylation product of metabolite M2 (M4).

In addition, the authors evaluated the formation of metabolite M2 measuring its plasma concentration in a control group of animals in comparison to rats treated with different antibiotics. Pharmacokinetic analyses revealed a significant decrease in systemic exposure to M2, with a nearly 60 % decrease in the faecal-mediated formation of M2 in antibiotic-treated animals. These findings suggested that the consumption of antibiotics may reduce the ability of GMB to metabolize orally administered drugs, with an impact on the systemic concentration of the drug itself or its metabolites.

5.4. Diclofenac (DCF)

DCF is an FDA-approved drug that falls under the class of NSAIDs. It is mainly used to treat acute and chronic pain related to inflammatory conditions, particularly those affecting the musculoskeletal system. These include ankylosing spondylitis, rheumatoid arthritis, and osteoarthritis. Actinic keratosis can be treated topically with it. Additionally, the FDA has approved DCF in ophthalmic medicine to treat photophobia, eye pain, and cataracts [120,121]. As other NSAIDs, DCF hampers the synthesis of prostaglandin by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2, respectively) with similar potency [122]. Its use is accompanied by well-known adverse events, including

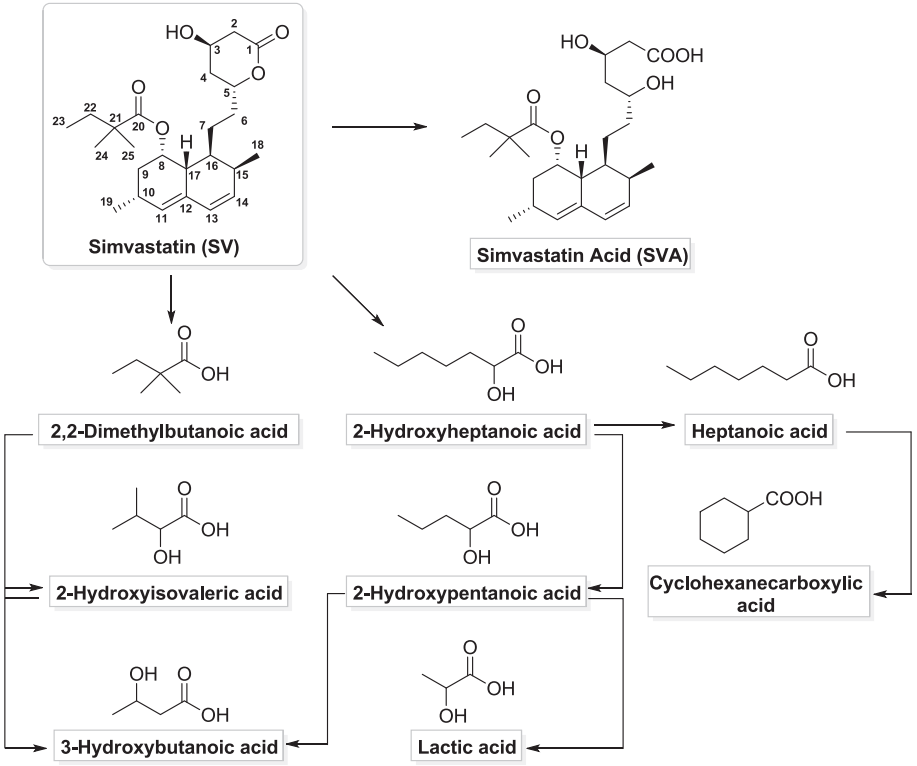


Fig. 5.4. Metabolites of SV, including SVA and various SCFA, generated by GMB activity.

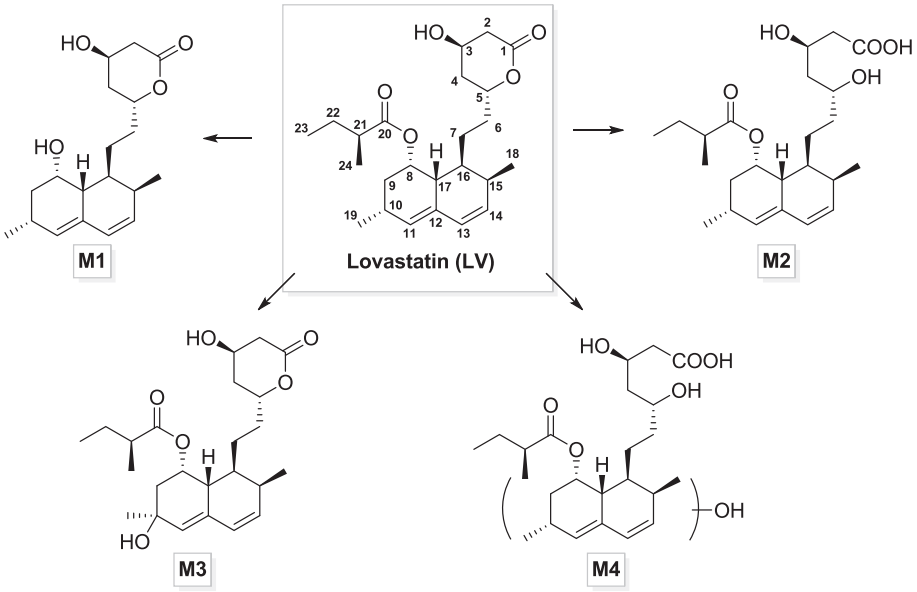


Fig. 5.5. Lovastatin (LV) gut-mediated metabolites.

increased risk of serious dose-related gastrointestinal, cardiovascular, and renal side effects [121].

Besides resulting in intestinal histological damage, DCF treatment can cause alterations in the expression of intestinal antioxidant genes and affect GMB composition in freshwater crayfish (*Procambarus clarkii*) [123]. The relative abundances of the predominant bacteria (e.g. *Firmicutes*, *Bacteroidetes*, *Actinobacteria*) showed significant changes at the phylum level. In rats, DCF-induced enteropathy is also associated with an increased abundance of *Proteobacteria* and *Bacteroidetes* and a significant decrease in *Firmicutes* [124,125]. NSAIDs treatment also induces an increase in Gram-negative bacteria, which can aggravate the intestinal damage caused by these remedies. The changes in microbial composition triggered by DCF do not seem to be linked to its direct antibacterial activity [126], which appears to be quite limited at therapeutic concentrations of the molecule in vivo. However, the co-administration of RX with DCF prevents NSAID-induced small bowel damages in rats, possibly because of the ability of this poorly absorbed antibiotic to target enteric bacteria and modulating mucosal inflammation [125].

Given the well-known involvement of COX-derived prostaglandins in

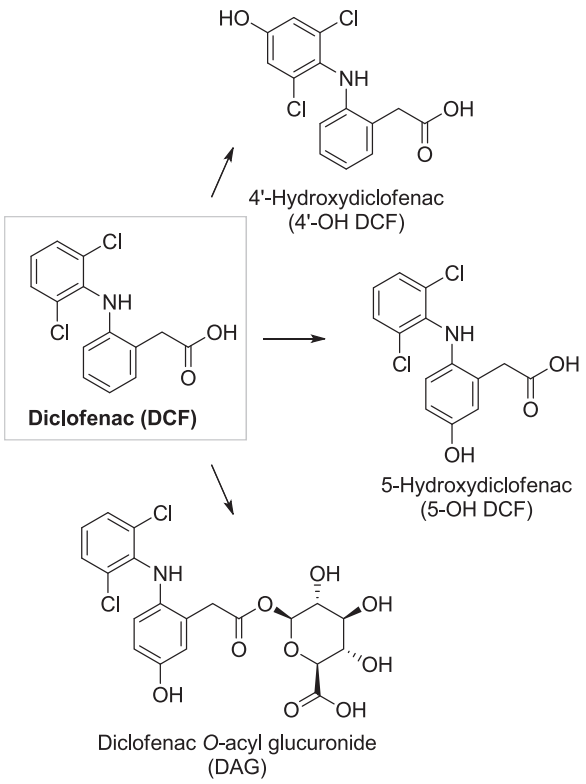


Fig. 5.6. Structures of diclofenac (DCF) and the major metabolites also derived from the intestine-mediated metabolism of the drug.

NDs, the potential effects of DCF and other NSAIDs have been intensively investigated in AD and PD. DCF has demonstrated unique benefits in AD compared to other NSAIDs. A cohort study by Stuve et al. associated DCF with a significantly lower frequency of AD [127], while Stopschinski et al. showed its ability to reduce microglial pro-inflammatory mediator release [74]. Additionally, DCF modulates pathways beyond inflammation, such as oxidative phosphorylation and ribosomal processes, suggesting broader neuroprotective effects [128]. Its interaction with the NLRP3/IL-1β pathway makes it an attractive candidate for further trials. NSAIDs treatment, including DCF, is associated with a lower PD risk, potentially through modulation of NF-κB signalling and reduction of neuroinflammation. NSAIDs inhibit α-synuclein fibril formation and destabilize preformed fibrils, a critical mechanism in the pathogenesis of PD and related disorders [129]. Although DCF is less potent than some NSAIDs in this regard, further preclinical and clinical exploration is needed to fully appreciate its potential as disease-modifying agent in NDs.

The activity of human GMB on DCF has been the object of different studies. An investigation carried out using precision-cut intestinal slices prepared from the jejunum of human donors as the ex vivo model, unveiled that the intestine is responsible for the production of 4′-OH DCF, 5-OH DCF, and diclofenac *O*-acyl glucuronide (DAG) as the main metabolites (Fig. 5.6). These also account for the major metabolic products occurring in the liver and circulating in plasma [130].

Human intestinal and liver microsomes express uridine diphosphate-glucuronosyltransferases 17 (UGT2B17) with high variability across the different populations. This enzyme has been shown to play a pivotal role in DCF glucuronidation in the intestine and variability in its abundance leads to significant differences in DAG formation and, hence, in DCF metabolism and pharmacokinetics [131]. Another possible explanation for the intestinal injury connected to the use of DCF is associated with the action of bacterial β-glucuronidase in the gut on DAG. Repeated exposure of enterocytes to the resulting product of DAG hydrolysis may result in local tissue damage and initiate enteropathy [132]. In fact, selective bacterial β-glucuronidase inhibitors reduce intestinal mucosa exposure to DCF and provide protection against DCF-induced enteropathy [133]. In addition, metabolites of DCF are largely excreted through bile, worsening intestinal DCF adverse events, especially in those patients recovering from surgical procedures [134].

6. Conclusions

The growing body of evidence linking the GMB and the gut-brain axis to neurodegenerative processes underscores the importance of considering intestinal metabolism in modern therapeutic approaches. Although drugs commonly used for the treatment of NDs are traditionally evaluated in terms of absorption, distribution, metabolism, and excretion, the influence of their interaction with the GMB remains an often-overlooked aspect. The evidence presented here on the modulation of the GMB by different compounds often used in subjects with neurological diseases points to the clinical relevance of the association between the GMB and the clinical trajectories of these patients. Indeed, understanding the role of the gut not only in drug absorption but also in their metabolic transformation and impact on the CNS represents a crucial challenge for future research and highlights the need to develop a strong interdisciplinary approach to develop innovative strategies to address the complex interactions between drugs, GMB, and neurological disorders, with the potential to significantly enhance the quality of life for patients.

Abbreviations

3M-4-TMAB	3-methyl-4-(trimethylammonio)butanoate
4-TMAP	4-(trimethylammonio)pentanoate
AD	Alzheimer's disease
ALC	acetyl-L-carnitine
AV	atorvastatin
Aβ	Amyloid β
BBB	blood brain barrier
CNS	central nervous system
COMT	catechol-*O*-methyl transferase
COX	cyclooxygenase
CUMS	chronic unpredictable mild stress
Dadh	molybdenum cofactor–dependent dopamine dehydroxylase
DAG	diclofenac *O*-acyl glucuronide
DCF	diclofenac
DHPLA	3-(3,4-dihydroxyphenyl) lactic acid
DHPPA	3-(3,4-dihydroxyphenyl) propionic acid
ENS	enteric nervous system
ES	endogenous synthesis
FDA	food and drug administration
FMOs	liver flavin-containing monooxygenase
GMB	gut-microbiota
HNK	honokiol
IBS	irritable bowel syndrome
IL	interleukin
LC	L-carnitine
LCIG	levodopa-carbidopa intestinal gel
LD	levodopa
LDL	low-density lipoprotein
LV	lovastatin
MA	malic acid
MAM	mucous-associated microbiome
ND	neurodegenerative disease
NSAID	non-steroidal anti-inflammatory drug
PD	Parkinson's disease
PLP	pyridoxal phosphate
RCT	randomized clinical trial
RV	rosuvastatin
RX	rifaximin

SARs	structure-activity relationships
SCFA	short-chain fatty acid
SNP	single-nucleotide polymorphism
SV	simvastatin
SVA	simvastatin acid
TDC	tyrosine decarboxylase
TJ	tight junction
TMA	trimethylamine
TMAO	trimethylamine N-oxide
TNF	tumour necrosis factor
UGT2B17	uridine diphosphate-glucuronosyltransferases 17
γ-BB	γ-butyrobetaine

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Declaration of competing interest

The authors report no conflicts of interest in this work. All authors have revised and approved the final version of the article, including the authorship list.

Data availability

Review Article. Data are available in the cited literature.

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