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Lawson K

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Editor-in-Chief of *World Journal of Pharmacology*, Nam Deuk Kim, PhD, Professor, (E-mail:nadkim@pusan.ac.kr) College of Pharmacy, Pusan National University, Busan 46241, South Korea

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Pharmacology and clinical applications of flupirtine: Current and future options

Kim Lawson

ORCID number: Kim Lawson
(0000-0002-5458-1897).

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Kim Lawson, Department of Biosciences and Chemistry, Biomolecular Sciences Research Centre, Sheffield Hallam University, Sheffield S1 1WB, United Kingdom

Corresponding author: Kim Lawson, PhD, Senior Lecturer, Department of Biosciences and Chemistry, Biomolecular Sciences Research Centre, Sheffield Hallam University, City Campus, Howard Street, Sheffield S1 1WB, United Kingdom. k.lawson@shu.ac.uk
Telephone: +44-114-2253057
Fax: +44-114-2253066

Abstract

Flupirtine is the first representative in a class of triaminopyridines that exhibits pharmacological properties leading to the suppression of over-excitability of neuronal and non-neuronal cells. Consequently, this drug has been used as a centrally acting analgesic in patients with a range of acute and persistent pain conditions without the adverse effects characteristic of opioids and non-steroidal anti-inflammatory drug and is well tolerated. The pharmacological profile exhibited involves actions on several cellular targets, including Kv7 channels, G-protein-regulated inwardly rectifying K channels and γ -aminobutyric acid type A receptors, but also there is evidence of additional as yet unidentified mechanisms of action involved in the effects of flupirtine. Flupirtine has exhibited effects in a range of cells and tissues related to the locations of these targets. In addition to analgesia, flupirtine has demonstrated pharmacological properties consistent with use as an anticonvulsant, a neuroprotectant, skeletal and smooth muscle relaxant, in treatment of auditory and visual disorders, and treatment of memory and cognitive impairment. Flupirtine is providing important information and clues regarding novel mechanistic approaches to the treatment of a range of clinical conditions involving hyper-excitability of cells. Identification of molecules exhibiting specificity for the pharmacological targets (e.g., Kv7 isoforms) involved in the actions of flupirtine will provide further insight into clinical applications. Whether the broad-spectrum pharmacology of flupirtine or target-specific actions is preferential to gain benefit, especially in complex clinical conditions, requires further investigation. This review will consider recent advancement in understanding of the pharmacological profile and related clinical applications of flupirtine.

Key words: Flupirtine; Kv7 channels; GABA_A receptors; Analgesia; Seizures; Neuroprotection; Myotonia; Memory; Tinnitus

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Core tip: Flupirtine exhibits pharmacological properties due to actions on Kv7 channels, G-protein-regulated inwardly rectifying K channels and γ -aminobutyric acid type A receptors leading to the suppression of over excitability of neuronal and non-neuronal cells. Consequently flupirtine has demonstrated efficacy consistent with use as an analgesic, an anticonvulsant, a neuroprotectant, skeletal and smooth muscle relaxant, in treatment of auditory and visual disorders, and treatment of memory and cognitive impairment. Flupirtine is providing important information and clues regarding novel mechanistic approaches to the treatment of a range of clinical conditions involving hyper-excitability of cells.

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INTRODUCTION

Flupirtine is the first representative in a class of triaminopyridines that exhibits pharmacological properties leading to the suppression of neuronal over-excitability. Consequently, this molecule has demonstrated to be beneficial in treating patients with a range of pain conditions^[1-4]. Flupirtine relative to other analgesics on the market exhibits unique chemical structure and modes of action that contribute to a preferable pharmacological profile. It does not possess the adverse effects characteristic of opioids and non-steroidal anti-inflammatory drug and is well tolerated.

Flupirtine has been classified as a selective neuronal potassium channel opener due to action on voltage-gated K channels belonging to the Kv7 subfamily (with selectivity for the Kv7.2-Kv7.5 isoforms) and G-protein-regulated inwardly rectifying K (GIRK) channels^[5,6]. Channel activation by flupirtine will lead to hyperpolarization of the membrane potential and attenuates the generation of action potentials, thus offering a novel therapeutic approach for diseases associated with cellular hyperexcitability^[5].

Flupirtine has been the subject of a few good reviews describing its history and clinical profile as a treatment of pain^[1-4]. In addition, flupirtine has been used as a pharmacological tool to gain greater understanding of Kv7 channels as a therapeutic target^[7-9]. The aim of this review is to consider the advancement in recent understanding of the pharmacological profile and related clinical applications of flupirtine. MEDLINE database, Web of Science and Google Scholar were used to identify relevant studies and publications up to July 2018 using the term “flupirtine”. Flupirtine exhibits an interesting pharmacological profile that offers clues of potential targets that merit investigation as novel therapeutic approaches to a range of clinical conditions.

ANALGESIA

Pain relieving activity in various animal models and humans has been demonstrated with flupirtine a non-opioid analgesic without anti-inflammatory or antipyretic properties^[1-3]. Effective analgesia by flupirtine has been demonstrated in a range of persistent pain conditions such as musculoskeletal pain, postoperative pain, migraine and neuralgia^[2,3,10,11]. These effects of flupirtine are associated with restoration of normal sensitivity of over-excitability nociceptive pathways and inhibition of the stimulation of nociceptive neurons by factors such as inflammatory mediators (e.g., bradykinin)^[12-15]. In small fibre neuropathy the efficacy of flupirtine was reported to be sufficient to lead to the discontinuation of first-line drug treatments, such as gabapentin and amitriptyline, which are often associated with adverse effects or unsatisfactory pain relief^[16].

Flupirtine stabilizes the membrane resting potential by activating KCNQ (Kv7) potassium channels generating a neuronal hyperpolarizing current (M-current)^[5]. Activation of potassium channels will lead to an indirect N-methyl-D-aspartate (NMDA) receptor antagonism, thus reducing hyperexcitation of nociceptive neurons. In addition, Mg²⁺ block on NMDA receptors is maintained by an oxidizing action of

flupirtine at the redox site of the receptor consistent with an indirect inhibition^[17]. There is however no interaction with the binding site of the NMDA receptor^[6].

Kv7 channels encompass five members of which Kv7.2-Kv7.5 are expressed and distributed throughout peripheral nerves and the CNS, and co-assemble to form either homo- or hetero-tetramers^[18,19]. Agonist action at (Gq/11) G protein-coupled receptors, such as acetylcholine at muscarinic receptors, can inhibit channel activity. Kv7 channels are expressed in neurons forming the nociceptive pathways, such as central terminals of primary afferents and dorsal horn neurons within the spinal cord^[20]. Long-term downregulation of Kv7 subunits following neuropathic injury, whether due to trauma or inflammation, has been proposed to contribute to hyperexcitability of sensory fibres^[21]. Increased levels of repressor element1-silencing transcription factor leading to reduced density of Kv7.2, Kv7.3 and Kv7.5 is a delayed feature of neuropathic injury with probable involvement in the maintenance rather than the initiation of pain^[22]. The decreased channel density was functionally compensated by the activation of residual Kv7 channels by flupirtine resetting neurons to a low-excitability state and suppressing pain^[21]. Flupirtine exhibits efficacy on all four subunits, Kv7.2, Kv7.3, Kv7.4 and Kv7.5, with an apparent preference for Kv7.3. Interestingly, flupirtine appeared to evoke an effect specifically in injured neurons and not uninjured fibres^[21]. Associated with the analgesic activity of flupirtine is the ability of inhibiting the release of neurotransmitters, such as calcitonin-gene related peptide, from the brainstem following the opening of Kv7 channels^[23].

Flupirtine has been found to act simultaneously on Kv7 channels and γ -aminobutyric acid type A (GABA_A) receptors which are both involved in the control of nociception^[24]. Thus, the combined stimulatory action in pain neural circuits may contribute to the analgesic activity of flupirtine. The subunit composition of the GABA receptor defines specific pharmacological characteristics such that benzodiazepines modulate γ 2-subunit containing receptors, whereas δ -subunits are highly sensitive towards neurosteroids^[25,26]. Preferential action by flupirtine at δ -subunit containing GABA_A receptors over γ -containing GABA_A receptors has been demonstrated^[27]. The presence of α 4 and α 6 subunits renders δ -subunit containing GABA_A receptors insensitive to benzodiazepines^[28,29]. Thus, the pharmacological properties of flupirtine due to interaction with GABA receptors will have a profile that differs from that exhibited by benzodiazepines. Although the induction of addictive behaviours in certain drugs is associated with agonism at GABA_A receptors, such properties of flupirtine have had limited anecdotal reporting^[30,31].

Synergistic or additive effects with other analgesics have been suggested to be likely for molecules that inhibit the NMDA receptor^[32]. Flupirtine and opioids have been reported to exhibit synergistic analgesic interactions^[32,33]. Synergistic interactions have also been observed with flupirtine and the atypical opioids, tramadol and tapentadol, which exhibit the dual mechanisms of action of μ -opioid receptor agonism and inhibition of noradrenaline reuptake^[33,34]. Such co-administration will offer benefits such as enhanced analgesic efficacy and prolonged analgesic duration, relative to the minimization of adverse effects and reduction in opioid tolerance.

ANTICONVULSANT

Disruption of the excitatory-inhibitory balance in brain neural networks leading to synchronous activation and recurrent seizures characterises epilepsy. Consistent with its ability to suppress neuronal hyperexcitability flupirtine has demonstrated anticonvulsant activity in the Antiepileptic Drug Development program^[7].

Studies have demonstrated flupirtine to be very effective against neonatal seizures induced, for example, by hypoxia/ischaemic injury or chemoconvulsants, with efficacy preferable to current anticonvulsant therapies, such as phenobarbital and diazepam^[35-37]. Pretreatment with flupirtine prevented development of neonatal electroclinical seizures, whilst administration after the generation of a seizure prevented subsequent seizures and thereby reduced overall seizure burden. In the immature brain compared to that of an adult the GABAergic inhibitory system is underdeveloped and has fewer GABA_A receptors, different GABA_A receptor subunit composition (*e.g.*, low levels of delta subunits) and lower GABA-mediated currents^[38,39]. A decreased efficacy of drugs that target GABA_A receptors such as phenobarbital against neonatal seizures is consistent with the brain underdevelopment^[38,39]. As described previously, flupirtine evokes stabilization of neuronal hyperexcitability due to activation of Kv7 and GIRK channel activity, and potentiation of GABA responses of the δ -subunit containing GABA_A receptor^[24,27]. Although the mechanism responsible for the anti-neonatal seizure activity of

flupirtine is unknown, involvement of Kv7 activation is the more likely explanation of providing greater efficacy than and thereby advantage over GABA receptor modulating drugs.

In neonatal rats, flupirtine induced a burst suppression-like electroencephalography (EEG) pattern^[36]. Burst suppression is when high voltage activity alternating with periods of no activity in the brain characterize the EEG pattern. Refractory status epilepticus can be terminated by the induction of the burst suppression pattern by midazolam, and as observed with flupirtine^[40]. In rat models of established status epilepticus initial data indicated that the combination of flupirtine and diazepam terminated seizures preferentially to either drug alone, however efficacy of flupirtine alone appeared dependent on the animal model^[41]. Thus, the potential benefit in the clinic available from treatment with flupirtine may be dependent on the underlying aetiology of established status epilepticus.

Febrile seizures are the most common convulsive events in infants and young children where recurrence may be a risk factor for greater likelihood of later epilepsy^[42]. Repetitive febrile seizures (RFS) have been associated with impaired hippocampus-dependent long-term memory^[43]. Current anti-convulsant drugs, including diazepam, phenobarbital and sodium valproate, although have proven effective at reducing seizure recurrence are limited due to adverse effects^[44]. In a rat model of RFS, flupirtine suppressed seizures and reduced risk of further seizures^[45]. Further, flupirtine was effective against RFS-induced learning and memory impairment and reduced RFS-induced neuronal degeneration. In this RFS model improvement due to flupirtine treatment was greater than that observed with current treatment for recurrent febrile seizures, phenobarbital^[45]. Activation of Kv7 channels is the probable property responsible for the efficacy of flupirtine for the treatment of RFS. Consistent with this conclusion is the observation that the expression level of Kv7.2 subunits is low in neonatal neurons and after the first post-natal week increases, which inversely correlates with the incidence of febrile seizures decreasing with age^[46].

NEUROPROTECTION

Neuroprotective activity has been exhibited by flupirtine in a variety of neurodegenerative disease models and clinical trials with suggestion of utility as a therapeutic approach in conditions such as Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jakob disease, prion disease, age-related macular degeneration and Batten disease^[2-4,47,48]. Indirect antagonism of the NMDA receptor and thereby glutamate-induced intracellular Ca^{2+} increase, upregulation of the antiapoptotic protein B-cell lymphoma 2 (Bcl-2) and antioxidant activity via increased glutathione levels and reduced reactive oxygen species levels have all been suggested to be involved in the neuroprotective properties of flupirtine^[2-4].

In experimental models of stroke flupirtine evoked neuroprotection when administered before or up to 9 hours post induction of cerebral ischaemia^[49-51]. An important signalling pathway contributing to post-ischaemic proteolysis and cell death is an NMDA-induced intracellular calcium increase leading to activation of calpain^[52]. Calpain is involved in the degradation of signal-transducer-and-activator-of-transcription-6 (STAT6) which in healthy brains inhibits c-Jun-N-terminal kinases (JNK) and nuclear factor- κB (NF- κB) signalling pathways which are critical to the progression of ischaemic brain injury^[51]. As a consequence of indirect NMDA receptor antagonism flupirtine at clinically relevant concentrations reduces the calcium dependent calpain activation and restores the STAT6-induced inhibition of JNK and NF- κB pathways and proteasomal activity^[51]. Thus, following flupirtine treatment infarct volumes were reduced, the blood brain barrier integrity stabilized and the inflammatory response and oxidative stress within the ischaemic lesion site reduced.

Chronic stress increases the susceptibility of neurons in the brain to injury with the induction of apoptosis particularly within the hippocampus, which has been proposed to contribute to impaired brain function and stress-related cognitive deficits^[53]. In a chronic stress model, flupirtine prevented impairment of spatial learning and memory, alleviated neuronal apoptosis and the reduction of dendritic spine density in the hippocampus^[54]. Flupirtine reversed the chronic stress-induced increased expression of the pro-apoptotic regulator Bax, inactivation of the protein kinase B (Akt)/glycogen synthase kinase-3 β (GSK-3 β) pathway, which regulates learning and memory, synaptic plasticity and cell survival, and reduction in the extracellular signal-regulating kinase 1/2 signalling pathway, which plays a role in cognitive processing^[54]. The role of Kv7 channels and/or GABA_A receptors in the effects of flupirtine in chronic stress however need clarification. Interestingly,

flupirtine has also been shown to prevent acute stress-induced impairment of spatial memory retrieval and hippocampal long-term potentiation^[55]. Activation of Kv7 channels by flupirtine was suggested to be responsible for the reduction in the acute stress-induced impaired memory formation.

Bcl-2 protein complexes with beclin 1 leading to an inhibition of autophagy, thus raised expression of Bcl-2 will influence proteostasis and cell death in neurodegenerative diseases^[56]. The Prp106-126 fragment of the prion protein, which is toxic to cortical neurons and involved in the development of prion diseases, reduced levels of the anti-apoptotic proto-oncogene Bcl-2 and of glutathione^[57]. Flupirtine blocked the decrease in glutathione and induced the expression of Bcl-2 reducing cell toxicity due to prion protein exposure^[57]. Consistent with these findings the cognitive decline in patients with Creutzfeldt-Jakob disease, in a randomized double-blind clinical trial, was decreased following treatment with flupirtine although there were no significant effects on survival^[58].

SKELETAL MUSCLE RELAXANT

Flupirtine evokes a reduction in skeletal muscle rigidity and akinesia by the suppression of spinal mono- and polysynaptic reflexes mediated by NMDA receptors^[59,60]. The monosynaptic Hoffmann reflex (H-reflex), which does not involve NMDA receptors, was not influenced by flupirtine^[59]. These properties of flupirtine are compatible as a therapeutic approach to the treatment of muscle rigidity, spasticity and related musculoskeletal conditions.

The pharmacological properties of flupirtine have also been identified useful in the treatment of myotonia^[61,62]. Myotonia and myotonic membrane hyperexcitability induced by anthracene-9-carboxylic acid in murine skeletal muscle was reduced by flupirtine following the activation of Kv7 channels^[61]. All KCNQ isoforms are expressed in murine myoblasts with Kv7.2 and Kv7.3 localized at the level of intracellular striations and Kv7.4 subunits restricted to the sarcolemmal membrane^[63]. Peripheral nerve hyperexcitability associated with neuromyotonia or myokymia is a consequence of inherited mutations in the human KCNA1 gene, which encode juxtaparanodal Kv1.1 channels, or acquired abnormal autoantibodies targeting Kv1 channel subunits^[64,65]. A synergy between Kv1 and Kv7 channels in regulating neuronal excitability has been observed and activation of Kv7 channels with flupirtine can reverse the axon hyperexcitability mediated by Kv1.1 channel deficiency^[62]. Thus, flupirtine could be a novel therapeutic approach to Kv1-related conditions involving peripheral nerve hyperexcitability.

SMOOTH MUSCLE RELAXATION

Kv7 channels have been identified as important regulators of contractility of vascular, gastrointestinal, urogenital, and tracheobronchial smooth muscle^[66]. In smooth muscle cells, Kv7 channels are basally active contributing to stabilizing the resting membrane potential at lower levels and counter depolarizing stimuli, thus reducing cell excitability and contractility. Kv7 channels contribute to the resting membrane potential in smooth muscle cells due to their slow inactivation and low voltage threshold for activation^[66].

It is well established that resting membrane potential and contractility in various blood vessels is regulated by Kv7 channels^[67]. Expression of KCNQ1, KCNQ4 and KCNQ5 has been reported in a diversity of human, rat and mouse arteries and veins, with KCNQ2 and KCNQ3 expression observed less frequently^[66-68]. Many pathological conditions, such as pulmonary hypertension and hyperglycaemia, have been associated with altered expression and function of Kv channels in coronary artery myocytes^[69-71]. In addition, reduced expression of Kv7.4 channels have been observed in coronary, renal, and mesenteric arteries of hypertensive rats^[72]. Flupirtine evoked concentration-dependent relaxation of rat left and right coronary arteries, with an increase in potassium channel current amplitude and membrane hyperpolarization in myocytes from left coronary arteries but not from right coronary arteries^[73]. The differential effects of flupirtine on coronary arteries may be associated with the expression of Kv7.5 being significantly higher in left than in right coronary arteries, whilst Kv7.4 expression was similar. The flupirtine-induced relaxation of porcine left circumflex coronary artery was reduced following endothelial denudation^[68]. The flupirtine-induced relaxant response in intact, but not that in artery denuded of endothelium, was inhibited by the non-selective Kv7 channel antagonist linopirdine consistent with the activation of Kv7 channels by flupirtine. In contrast, structurally

different Kv7 channels activators (S)-1, retigabine, BMS-254352 and ML213 evoked linopirdine-sensitive relaxations of precontracted porcine and rat coronary arteries that were not affected by removal of the endothelium^[74,75]. In porcine left coronary arteries immunohistochemical staining for Kv7.4 was prominent in the intimal (endothelial) layer, but less in the medial (smooth muscle) layer^[68]. Strong Kv7.4 immunostaining however was observed in the medial and intimal layers of porcine right coronary artery, and Kv7.5 immunostaining was strong only in the intimal layer with much weaker intensity in the intimal layer^[75]. The differential endothelial-dependent effects may be due to the distribution and density of channel subtype expression combined with potential subtype selectivity profile of flupirtine relative to other Kv7 channel activators. Thus, the vasorelaxant response to flupirtine in coronary arteries appears to involve endothelium based Kv7 channels and an as yet unidentified mechanism in the smooth muscle cells.

Flupirtine evoked pulmonary vasodilation in lungs from hypoxic rats but not from normoxic rats^[76]. Consequently, raised pulmonary vascular resistance due to hypoxia could be prevented and reversed by flupirtine^[76,77]. Hypoxia leads to the downregulation of Kv7.4, but not Kv7.1 nor Kv7.5, channels and smooth muscle cell depolarisation. Although the molecular target responsible for the actions of flupirtine have not been identified, activation of the residual Kv7.4 channels, of Kv7.5 channels or a combination of Kv7.4/7.5 needs further evaluation. The Kv7 activation exhibited by flupirtine would be a potential treatment approach for pulmonary hypertension.

Activation of Kv7 channels in bladder smooth muscle cells will dampen electrical activity and regulate excitability. In guinea pig bladder detrusor smooth muscle flupirtine hyperpolarized the cell membrane with a simultaneous cessation of spontaneous transient depolarizing electrical activity and suppression of myogenic spontaneous contractions^[78]. Takagi and Hashitani (2016) observed that flupirtine abolished spontaneous action potential discharge in guinea pig detrusor smooth muscle cells without hyperpolarization with the suggestion that only modest opening of Kv7 channels is required^[79]. Interestingly Kv7 channels were suggested to only be partial responsible for the flupirtine-induced reduction of the amplitude of spontaneous action potentials associated with spontaneous activity of guinea pig muscularis mucosae^[80]. Flupirtine, following Kv7 channel activation, evoked relaxations of the human detrusor muscle, of which overactivity is frequently present in overactive bladder syndrome^[81]. As with the guinea pig smooth muscle cells, all five KCNQ genes which encode Kv7.1-7.5 channels are expressed in the human detrusor with the Kv7.4 channel subunit showing the highest expression level^[81,82]. Thus, selective Kv7.4 channel activators would be preferential novel therapeutic treatments of urinary bladder overactivity conditions. Human overactive bladder or detrusor overactivity in animal models are characterized by increases in spontaneous activity, thus ideal treatment strategy of overactive bladder would be modulation of the spontaneous excitability^[83].

All KCNQ isoforms, except KCNQ5, are expressed in human myometrial smooth muscle tissue with a predominance of KCNQ4 and KCNQ1^[84]. Thus, the expression profile of KCNQ genes in the uterus resembles other smooth muscles. Although all KCNQ isoforms were expressed in myometrium from pregnant mice in early and late gestation, KCNQ1, KCNQ2, KCNQ4 and KCNQ5 all up-regulated in late pregnancy^[83]. Flupirtine suppressed myometrial contractile activity, with a partial effect in early gestation animals and a profound action in late gestation mice^[84]. Although no teratogenic effects of flupirtine are known or have been reported in animal studies, the potential risk for humans is unknown^[85]. Thus, Kv7 channel activation by flupirtine could be a novel approach for tocolysis for use in human preterm labour.

Flupirtine has exhibited relaxing properties of gastrointestinal smooth muscle such as rat stomach and human taenia coli^[86,87]. In gastrointestinal tract tissues from animals and humans Kv7.4 and Kv7.5 isoforms had the highest expression levels, with the former being the predominant channel^[88]. Thus, this property of flupirtine would be relevant for the treatment of gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome^[89].

Flupirtine has been shown to enhance Kv7 currents in guinea pig airways smooth muscle cells and evoke relaxation of precontracted human airways thereby indicating utility as an effective bronchodilator^[89]. In human airways smooth muscle cells expression of KCNQ1, KCNQ4 and KCNQ5 has been reported, whilst KCNQ2 and KCNQ3 were undetectable^[90]. In mouse and rat tracheal smooth muscle cells where the expression of KCNQ subtypes reflects that observed in human tissue, flupirtine evoked Kv7 channel dependent hyperpolarization and relaxation^[91]. Interestingly, KCNQ2 was the most abundant isoform detected in guinea pig airways smooth muscle cells, suggesting this species may not predict clinical efficacy of flupirtine and similar drugs^[89].

AUDITORY AND OCULAR PROPERTIES

Reduction in Kv7.2 and Kv7.3 channel activity leading to hyperactivity in the dorsal cochlear nucleus (an auditory brainstem nucleus) has been associated with the initiation of the auditory disorder tinnitus^[92]. Flupirtine inhibited the spontaneous activity in mouse auditory cortical networks which was suggested to involve Kv7 channel activation^[93]. These findings are consistent with the pharmacological properties of flupirtine being relevant to the treatment of tinnitus.

Retinal ganglion cell hyperactivity is associated with photoreceptor dystrophic disorders and blindness. Flupirtine decreased spontaneous firing and sensitivity to optogenetic stimulation in mice retinal ganglion cells sensitive to channelrhodopsin2 stimulation^[94-96]. Thus, an increase in activity or expression of Kv7 potassium channels, the specific subtypes as yet have not been identified, in retinal amacrine cells would result in decreased spontaneous activity and could be a therapeutic approach to visual disorders.

ADVERSE EFFECTS AND TOLERABILITY

Most common adverse effects associated with flupirtine treatment (*i.e.*, dizziness, drowsiness, nausea, dry mouth, heartburn, fatigue, headache) which occurred within 6 mo of treatment were reported to be mild and transient^[2-4]. Consequently flupirtine has been viewed as well tolerated as reflected by regular use since it was first approved in the 1980s.

Long-term flupirtine treatment has been associated with liver injury with rare cases of liver failure and fatality^[97,98]. Complex hepatic metabolism of flupirtine involving N-glucuronidation, hydrolysis and N-acetylation leads to the formation of an active metabolite D13223^[99,100]. Flupirtine is hydrolysed by carboxylesterase and N-acetyltransferase 2 (NAT2) appears responsible for the acetylation of the hydrolysed metabolite of flupirtine^[100]. Reactive quinone diimines, which conjugate with glutathione, however appear to also be formed from the hydrolysed metabolite through non-enzymatic conversion. The quinone diimine intermediates of flupirtine, like the quinone imines intermediates formed with paracetamol and diclofenac, are candidates for the cellular toxicity^[100-102]. Thus, acetylation by NAT2 or conjugation by glutathione detoxify by preventing the build-up of quinone diimines^[100]. The genetic polymorphisms of NAT2 which show a large inter-individual variability due to genetic polymorphisms and thereby variation in acetylation efficiency could be critical for flupirtine-induced liver injury^[100,103]. Humans that exhibit high carboxylesterase activity with slow NAT2 acetylation and have low hepatic glutathione stores appear to be highly susceptible to flupirtine-induced liver injury^[100]. Other risk factors have been proposed such as single nucleotide polymorphisms of human leukocyte antigen and myeloperoxidase^[99,104].

The flupirtine related hepatotoxicity leads to extensive perivenular (zone 3) necrosis with infiltration of ceroid-pigment containing macrophages and lymphocytes^[97]. Vulnerability of zone 3 hepatocytes to necrosis appears to be related to stores of glutathione, which detoxifies the reactive quinone diimines, being depleted with a reduced ability to be replenished^[97]. N-acetylcysteine, essential for the replenishment of depleted glutathione stores, in combination with prednisolone treatment in patients with flupirtine-induced liver injury has been shown to improve serum biochemistries including alanine aminotransferase and aspartate aminotransferase^[105].

The potential of flupirtine-induced liver injury, although rare, led to the European Medicines Agency's Pharmacovigilance Risk assessment committee issuing risk minimization measures (RMM)^[106-108]. As a consequence of limited adherence to the RMM by prescribers flupirtine containing medications were withdrawn from the European market^[106].

CONCLUSION

Flupirtine has been used extensively for more than 30 years in the management of pain^[2-4]. Effectiveness has been demonstrated in a range of neuronal and non-neuronal biological systems consistent with therapeutic potential as treatment of a diversity of clinical conditions (Table 1). The pharmacological profile exhibited involves actions on several cellular targets, including Kv7 channels, GIRK channels and GABA_A receptors. Although many effects can be accounted for as the result of activation of Kv7 channels, there is suggestion that yet unidentified mechanisms of action may also

be involved in the effects of flupirtine.

Flupirtine is providing important information regarding novel mechanistic approaches to the treatment of different clinical conditions. Molecules exhibiting specificity for the pharmacological targets (*e.g.*, Kv7 isoforms) involved in the actions of flupirtine will provide further insight into their clinical potential. Whether the broad-spectrum pharmacology of flupirtine or target-specific actions is preferential to gain benefit, especially in complex clinical conditions, requires further investigation.

Whilst the rare hepatotoxicity associated with flupirtine may limit its use, at risk subjects can be identified by hepatic enzyme screening and risk can be limited by glutathione supplement to replenish stores. Investigation of the oxidative metabolites of flupirtine have been reported to contribute to the activation of Kv7.2/Kv7.3 channels mechanism of action, but not to hepatotoxicity^[109]. Thus, the analgesic activity, at least, and cytotoxicity in hepatocytes appear separable in this class of drugs.

In conclusion, flupirtine, in addition to use as an analgesic, shows potential for repurposing as a novel approach to clinical conditions such as tinnitus, visual impairment, memory impairment, requiring neuroprotection or requiring smooth muscle relaxation. Identifying new uses for existing drugs or repurposing bypasses time and cost of drug development. Finally, the pharmacology of flupirtine can also stimulate the identification of next generation related drugs exhibiting target specific actions.

Table 1 Summary of pharmacological profile and potential clinical applications of flupirtine

	Molecular target	Clinical condition	Ref.
Analgesia	Kv7.2, Kv7.3, Kv7.5 channels	Persistent pain	[2,16,24,27]
	GIRK channels	Acute pain	
	GABA _A receptors		
Anticonvulsant	Kv7.2, Kv7.3, Kv7.5 channels	Neonatal seizures	[33-35,38,39,43]
	GIRK channels	Repetitive febrile seizures	
Neuroprotection	Kv7 channels - indirect NMDA receptor antagonism	Stroke	[47-49,52,53,55,56]
	Bcl-2 protein	Chronic stress	
	Glutathione	Prion diseases	
		Parkinson's disease	
		Alzheimer's disease	
Skeletal muscle relaxant	Kv7.2, Kv7.3, Kv7.4 channels	Spinal Polysynaptic reflexes	[60-63]
		Myotonia	
		Parkinson's disease	
Vascular smooth muscle relaxation	Kv7.4, Kv7.5 channels	Coronary artery disease, angina	[69,74-76]
	Unidentified mechanism	Pulmonary hypertension	
Urinary bladder smooth muscle relaxation	Kv7.4 channels	Overactive bladder	[78-80]
		Detrusor overactivity	
Myometrial smooth muscle relaxation	Kv7 channels	Preterm labour (tocolysis)	[83]
Gastrointestinal smooth muscle relaxation	Kv7.4, Kv7.5 channels	Functional dyspepsia	[84-86]
		Irritable bowel syndrome	
Respiratory smooth muscle relaxation	Kv7.4, Kv7.5 channels	Asthma	[88,89]
Auditory stabilization	Kv7.2, Kv7.3 channels	Tinnitus	[91]
Retinal stabilization	Kv7 channels	Photoreceptor dystrophic disorders	[92-94]
		Age related macular degeneration	
		Blindness	
Memory formation	Kv7 channels	Learning and memory impairment	[52,53]
		Cognitive processing	

GIRK: G-protein-regulated inwardly rectifying K⁺ channels; GABA: γ-aminobutyric acid; NMDA: N-methyl-D-aspartate.

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REVIEW

- 14 Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine

Maideen NMP

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Editorial Board Member of *World Journal of Pharmacology*, Vishal Sharma, MD, Assistant Professor, Assistant Technical Editor, Doctor, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.

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Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine

Naina Mohamed Pakkir Maideen

ORCID number: Naina Mohamed Pakkir Maideen (0000-0002-6950-9783).

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Naina Mohamed Pakkir Maideen, Department of Pharmacy, Dubai Health Authority, Dubai 4545, United Arab Emirates

Corresponding author: Naina Mohamed Pakkir Maideen, PhD, Pharmacist, Department of Pharmacy, Dubai Health Authority, Al Maktoum Bridge Street, Dubai 4545, United Arab Emirates. nmmaideen@dha.gov.ae

Telephone: +971-42-164952

Fax: +971-42-244302

Abstract

Tobacco smoking is a global public health threat causing several illnesses including cardiovascular disease (Myocardial infarction), cerebrovascular disease (Stroke), peripheral vascular disease (Claudication), chronic obstructive pulmonary disease, asthma, reduced female infertility, sexual dysfunction in men, different types of cancer and many other diseases. It has been estimated in 2015 that approximately 1.3 billion people smoke, around the globe. Use of medications among smokers is more common, nowadays. This review is aimed to identify the medications affected by smoking, involving Cytochrome P450 (CYP) and uridine diphosphate-glucuronosyltransferases (UGTs) enzymes and Nicotine. Polycyclic aromatic hydrocarbons (PAHs) of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1 and UGT enzymes. The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those enzymes, may need higher doses due to decreased plasma concentrations through enhanced induction by PAHs of tobacco smoke. The prescribers and the pharmacists are required to be aware of medications affected by tobacco smoking to prevent the toxicity-associated complications during smoking cessation.

Key words: Drug Interactions; Tobacco smoking; Cytochrome P450 enzymes; Uridine diphosphate-glucuronosyltransferases enzymes; Nicotine

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Core tip: Use of medications among smokers is more common, nowadays. This review is aimed to identify the medications affected by smoking, involving cytochrome P450 (CYP) and uridine diphosphate-glucuronosyltransferases (UGTs) enzymes and Nicotine. The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those

enzymes, may need higher doses due to decreased plasma concentrations through accelerated metabolism by Polycyclic aromatic hydrocarbons of tobacco smoke. The prescribers and the pharmacists are required to be aware of medications affected by tobacco smoking to prevent the toxicity-associated complications during smoking cessation.

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INTRODUCTION

Tobacco use is a global public health threat causing several illnesses including coronary heart disease, cancers of organs such as lungs, mouth, throat, esophagus, pancreas, etc., chronic obstructive pulmonary disease, asthma and premature deaths. The World Health Organization (WHO) estimated that over 7 million people die of tobacco related diseases, annually and it has been projected to kill 10 million users of tobacco a year, by 2030^[1]. Tobacco products are categorized majorly as smokeless tobacco and smoked tobacco. Various forms of smokeless tobacco include chewing tobacco, snus, moist snuff, dry snuff, gutka, loose leaf, twist and plug^[2] while the smoked tobacco products include cigarettes, cigars, bidis, kreteks, pipe tobaccos and water pipe tobaccos^[3].

In 2015, it has been estimated that approximately 1.3 billion people smoke, around the globe, and almost 80 percent of smokers live in Low or middle income countries (LMICs) such as Bangladesh, India, Indonesia, etc^[4]. In addition, over 8 million smokers are expected to be killed due to tobacco smoking every year globally, by the year 2030. Generally, tobacco smokers are expected to die 10 years earlier than non-smokers do.

Tobacco smoking is associated with various conditions such as cardiovascular disease [Myocardial infarction (MI)], cerebrovascular disease (Stroke), peripheral vascular disease (Claudication), chronic obstructive pulmonary disease, asthma, reduced female infertility, sexual dysfunction in men, different types of cancer and many other diseases^[5]. Maternal smoking during pregnancy affect the offspring in many ways including low birth weight, premature birth, still birth, fetal death, infant death, congenital heart defects, CNS effects, and respiratory complications^[6] while smoking related negative outcomes in mothers include placental abruption, placenta previa, premature rupture of membranes and ectopic pregnancy^[7].

Smoking can affect non-smokers through second hand smoke (SHS) and third hand smoke which can induce many health complications as the voluntary smoking does. SHS is the mixture of sidestream smoke (SSS) (-85%) and exhaled mainstream smoke (MSS) (-15%). SHS is also known as passive smoking, involuntary smoking or environmental tobacco smoke and SHS is reported to be associated with negative health effects such as increased incidence of cancers, asthma, respiratory infections, reduced lung growth in children, and many others^[8]. Thirdhand smoke (THS) is the residue of chemicals emitted from SHS, adhered to indoor surfaces like walls, furniture, carpet, blankets, and toys, and reemitted into the air^[9].

It has been estimated that tobacco smoke may contain 7357 chemical constituents^[10] including hazardous chemicals like polycyclic aromatic hydrocarbons (PAHs), ammonia, aromatic amines, phenols, carbonyls, hydrocyanic acid, and N-nitrosamines^[11] as a complex mixture of gases and particulate matter. The gaseous part of smoke contains the constituents such as Carbon monoxide, Hydrogen cyanide, and Aldehydes while the particulate matter containing Nicotine, PAHs, tars, pigments, trace elements, nitrosamines and insecticides^[12].

Interference of effects of one drug by the comedications or tobacco smoke is termed "Drug interaction". Increased incidence of adverse effects or decreased therapeutic efficacy of a drug resulting from a drug interaction is called "Adverse drug interaction"^[13,14]. As the number of comedications increases, the rate of drug interactions also increases^[15].

The cytochrome P450 (CYP) enzymes are hemoproteins, which are responsible for the metabolism of drugs and detoxification of xenobiotics. These enzymes are involved in the metabolism of drugs occurring through phase I (Oxidation) reactions.

The drugs or other substances (herbs, nutrients, supplements or tobacco smoke) inhibiting or inducing CYP enzymes, determine drug interactions^[16]. PAHs of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1^[17].

Uridine 5'-diphospho-glucuronosyltransferases [Uridine diphosphate (UDP)-glucuronosyltransferases, UGTs] are the family of enzymes catalyzing glucuronidation (Phase II (conjugative) reactions^[18]. PAHs of tobacco smoke have also been associated with the possible induction of UDP glucuronyltransferase (UGT) enzyme^[19].

The databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals (DOAJ) and reference lists were searched to identify related articles using the keywords such as Drug interactions, Tobacco Smoke, CYP enzymes, UGT enzymes and Nicotine.

Pharmacokinetic drug interactions associated with tobacco smoking are mediated through the stimulation of CYP and UGT enzymes while the pharmacodynamic interactions are mediated by Nicotine.

Pharmacokinetic interactions

The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those enzymes, may need higher doses due to decreased plasma concentrations through enhanced induction by PAHs of tobacco smoke (**Figure 1**).

Antipsychotics

The second-generation antipsychotics or atypical antipsychotics such as clozapine and olanzapine are very much useful in the treatment of schizophrenia compared to typical antipsychotics^[20]. Clozapine^[21] and olanzapine^[22] are primarily metabolized by CYP1A2 enzyme. It has also been reported that clozapine is metabolized by UDP glucuronosyltransferase 1A1 (UGT1A1) and UGT1A4^[23] while olanzapine is metabolized by UGT1A4^[24].

Approximately 70%-80% of patients with schizophrenia smoke^[25] and the plasma concentrations of clozapine^[26] and olanzapine^[27] could be lowered in smokers as the PAHs of tobacco smoke enhancing their metabolism mediated by CYP1A2 and UGT enzymes. Smoking cessation may elevate the risk of toxicity in patients taking clozapine^[28,29] and olanzapine^[30]. The habitual smokers taking clozapine or olanzapine, should be monitored after smoking cessation for symptoms related to their toxicity. The symptoms of clozapine toxicity^[31] include confusion, tachycardia, miosis, hyperthermia and leukocytosis and olanzapine toxicity^[28] include extrapyramidal symptoms. The patients stopped smoking may need dosage reduction of clozapine and olanzapine^[32].

The plasma concentrations of haloperidol found decreased in smokers and it is recommended to monitor the patients taking haloperidol while starting or stopping smoking^[33].

The clearance of Chlorpromazine has been increased by Cigarette smoking^[34] and the abrupt cessation of smoking resulted in worsening of adverse effects of chlorpromazine^[35].

Antidepressants

Tobacco smoking affects the bioavailability of antidepressants metabolized by CYP1A2 enzyme including Fluvoxamine, Duloxetine, Mirtazapine and Imipramine.

Fluvoxamine is an antidepressant, which belongs to Selective Serotonin Reuptake Inhibitor (SSRI) category. It has been reported to be metabolized by CYP enzymes like CYP1A2 and CYP2D6^[36]. Tobacco smoking may decrease the serum concentrations of fluvoxamine through the induction of CYP1A2-mediated metabolism^[37].

Duloxetine is categorized as a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. The CYP enzymes such as CYP1A2 and CYP2D6 are involved in the metabolism of duloxetine^[38]. PAHs of tobacco smoke decreases bioavailability of duloxetine by increasing the expression of CYP1A2 and metabolism of duloxetine^[39].

Mirtazapine is an atypical antidepressant and it is categorized as Tetracyclic antidepressant. The metabolism of mirtazapine is known to be mediated by CYP enzymes like CYP1A2, CYP2D6, and CYP3A4^[40]. In addition, UGT enzymes also found to be involved in the metabolism of mirtazapine to some extent^[41]. The serum levels of mirtazapine could be reduced in smokers due to the induction of metabolism mediated by CYP1A2 and UGT enzymes.

Imipramine is a tricyclic antidepressant and it is known to be metabolized primarily by CYP2C19 enzyme and by CYP1A2 enzyme to a smaller extent^[42]. Required doses of Imipramine might be increased in Smokers due to the induction

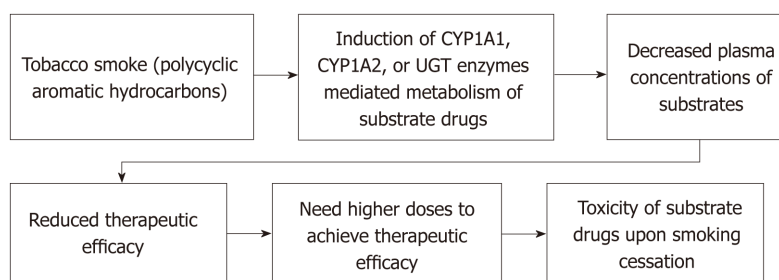


Figure 1 Pharmacokinetic drug interactions of smoking. Main mechanisms contributing to hyperkalemia with angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blocker (ARB) include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake. Main mechanisms contributing to hyperkalemia with ACEi/ARB include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake. Main mechanisms contributing to hyperkalemia with ACEi/ARB include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake.

CYP1A2-mediated metabolism^[43].

Theophylline and aminophylline

Theophylline is used to treat patients with airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) that are poorly controlled by bronchodilators, as an add-on therapy^[44]. Theophylline is effective as oral therapy and Aminophylline (Ethylenediamine salt of theophylline) is suitable for intravenous route.

CYP1A2 is known to be the major enzyme involved in the metabolism of theophylline and aminophylline^[45]. The plasma levels of theophylline was lesser in smokers^[46] as the PAHs of tobacco smoke accelerate the CYP1A2-mediated metabolism of theophylline. It has been reported that the plasma concentrations of theophylline was also decreased by secondhand smoke in adults^[47] and in children^[48] as the PAHs of sidestream smoke may induce the CYP1A2-mediated metabolism of theophylline.

The smokers may need higher doses of theophylline to compensate higher rate of clearance and smoking cessation in patients taking theophylline may result in theophylline toxicity as it has a narrow therapeutic index. The patients should be advised to seek medical attention if they develop the symptoms of theophylline toxicity such as seizures, hypotension, palpitations, nausea, vomiting, diarrhea, and others^[49].

Caffeine

Caffeine is metabolized predominantly by CYP1A2 enzyme^[50]. The CYP1A2-mediated metabolism of caffeine is enhanced in smokers^[51] and the regular smokers may consume more coffee or other caffeinated drinks due to increased clearance of caffeine^[52].

Riociguat

Riociguat is the first-in-class soluble guanylate cyclase (sGC) stimulator and it is useful to treat the patients with pulmonary hypertension^[53]. Riociguat is metabolized mainly by CYP enzymes including CYP1A1, CYP3A4, CYP3A5, CYP2C8, and CYP2J2^[54].

The plasma concentrations of riociguat was reduced in smokers^[55,56], as the PAHs content of tobacco smoke can induce CYP1A1-mediated metabolism of riociguat. The smokers may need higher doses of riociguat and it is recommended to do dosage adjustment of riociguat in patients stopped smoking.

Erlotinib

Erlotinib is an inhibitor of tyrosine kinase activity of Epidermal Growth Factor (EGF) receptor and it is approved to treat non-small-cell lung cancer^[57]. The metabolism of Erlotinib is mediated by CYP3A4 and CYP1A2 enzymes^[58].

The plasma concentrations of Erlotinib have been decreased significantly in smokers which might have occurred due to enhanced CYP1A2-mediated metabolism of Erlotinib by tobacco smoke^[59].

Tacrine

Tacrine is a centrally acting cholinesterase inhibitor and it is approved for the treatment of Alzheimer's disease^[60,61]. Tacrine is known to be metabolized by CYP1A2 enzyme^[62]. The serum concentrations of Tacrine might be decreased in smokers due to CYP1A2-mediated metabolism^[63].

Warfarin

Warfarin is an anticoagulant drug used widely to prevent thromboembolic events. It is a racemic mixture of two enantiomers including R-Warfarin and S-Warfarin. The R-warfarin is metabolized primarily by CYP1A2^[64].

Tobacco smoke may induce CYP1A2-mediated metabolism of R-Warfarin and decrease its efficacy. Smoking cessation may require close monitoring of International Normalised Ratio (INR) of patients taking warfarin^[65].

Propranolol

Propranolol is an antagonist of adrenergic beta receptors and it may be useful to treat various conditions including hypertension, angina pectoris, migraine, essential tremor, and many others. Propranolol has been identified as a substrate of CYP1A2 and CYP2D6 enzymes^[66].

The plasma concentrations of propranolol was diminished by smoking^[67] and it was noted higher in patients stopped smoking^[68].

Ropinirole

Ropinirole is a dopamine agonist and it is approved for the treatment of Parkinson's disease and restless legs syndrome^[69]. Ropinirole is metabolised principally by CYP1A2 enzyme^[70] and the plasma concentrations of Ropinirole may be decreased in smokers due to enhanced CYP1A2-mediated metabolism.

Smoking cessation in a patient taking Ropinirole resulted in increased rate of adverse effects such as excessive sweating at night, disturbed sleep with increased awakenings for several nights in a row^[71]. The dosage adjustments of Ropinirole may be required during smoking cessation.

Mexiletine

Mexiletine is a class 1B antiarrhythmic drug and it is a substrate of CYP1A2 enzyme^[72]. PAHs of tobacco smoke may induce the CYP1A2-mediated metabolism of mexiletine and it has been reported that the oral clearance of mexiletine was enhanced by tobacco smoking^[73].

Frovatriptan

Frovatriptan is an agonist of 5-hydroxytryptamine (5-HT) receptors and it is effectively used in the acute management of migraine and the prevention of menstrual migraines^[74]. Frovatriptan is principally metabolized by the CYP1A2 isoenzyme^[75]. The plasma concentrations of Frovatriptan was slightly decreased in tobacco smokers^[76].

Zolmitriptan

Zolmitriptan helps the patients with migraine by exhibiting agonistic activity on 5-HT receptors^[77]. It is primarily metabolised by CYP1A2 enzyme^[78]. PAHs of tobacco smoke may decrease plasma concentrations of Zolmitriptan by inducing the CYP1A2-mediated metabolism.

Alosetron

Alosetron is a potent and selective blocker of 5-HT₃ receptors and it is approved to treat the women with irritable bowel syndrome (IBS) having diarrhea as predominant bowel symptom^[79]. Alosetron is metabolised by various CYP enzymes including CYP1A2^[80]. Tobacco smoke may induce the CYP1A2-mediated metabolism of alosetron.

Flutamide

Flutamide is a nonsteroidal antiandrogen drug and it is used widely to treat carcinoma of prostate^[81]. CYP1A2 enzyme is involved principally in the metabolism of flutamide^[82]. CYP1A2-mediated metabolism of flutamide might be induced by PAHs of tobacco smoke.

Melatonin

Melatonin is a hormone, which regulates sleep-wake cycle and it is produced by the pineal gland. Exogenous melatonin is used as a dietary supplement to manage sleep disorders^[83]. The CYP enzymes including CYP1A2 and CYP1A1 are involved in the metabolism of exogenous melatonin^[84]. The plasma concentrations of exogenous melatonin was decreased in smokers^[85].

Ramelteon

Ramelteon is an agonist of melatonin receptors and it is approved to treat insomnia^[86]. Ramelteon is metabolised primarily by CYP1A2 enzyme^[87]. It has been postulated that smoking may decrease the levels of ramelteon by inducing CYP1A2-mediated metabolism.

Tasimelteon

Tasimelteon is an agonist of melatonin receptors (MT1 and MT2) and it is approved to treat non-24-hour sleep-wake disorder (N24HSWD). It is metabolised extensively by CYP1A2 and CYP3A4 enzymes^[88]. The exposure of tasimelteon was 40% decreased in cigarette smokers^[89].

Rasagiline

Rasagiline is a potent monoamine oxidase-B (MAO-B) inhibitor and it is indicated in the treatment of Parkinson's disease. It is metabolised mainly by CYP1A2 enzyme^[90]. The plasma concentrations of Rasagiline could be decreased in heavy smokers due to PAHs of tobacco smoke induced CYP1A2-mediated metabolism^[91]. heavy smokers, there is also a risk that rasagiline, AUC could be decreased due to induction of CYP1A2.

Tizanidine

Tizanidine is a centrally acting α_2 adrenergic receptor agonist and it is widely used as a skeletal muscle relaxant, to treat painful muscle spasms and spasticity^[92]. Tizanidine is substantially metabolised by CYP1A2 enzyme^[93,94]. The plasma concentrations and effects of Tizanidine could be decreased by smoking and the male smokers may require higher than average doses^[95].

Triamterene

Triamterene is a potassium-sparing diuretic and it is approved to treat hypertension and edema. Triamterene is exclusively metabolised by CYP1A2 enzyme^[96]. Cigarette smoking may induce the CYP1A2-mediated metabolism of triamterene and decrease its plasma concentrations.

Ropivacaine

Ropivacaine is an effective local anaesthetic which can be administered through epidural, intrathecal and other routes^[97]. Ropivacaine is metabolised extensively by CYP1A2 enzyme^[98] and it was noted that tobacco smoking increased the CYP1A2-mediated metabolism of ropivacaine^[99].

Methadone

Methadone is a synthetic opioid drug used to treat chronic pain. It is metabolized mainly by CYP3A4 and also by CYP1A2 and CYP2D6 enzymes in lesser extent^[100]. PAHs of tobacco can induce the CYP1A2-mediated metabolism of methadone and decrease its plasma concentrations.

Methadone toxicity (Decreased respirations and altered mental status) has been reported in a patient stopped smoking while being on methadone maintenance dose to treat chronic back pain^[101]. The prevalence of smoking is higher (85%-98%) in patients taking methadone as a maintenance therapy^[102]. Monitor the symptoms of methadone toxicity when the patients stopped smoking and the dose of methadone may need to be adjusted.

Hormonal replacement therapy

Tobacco smoke can increase the hepatic clearance of orally administered estrogens and reduce the therapeutic efficacy of hormonal replacement therapy (HRT) such as reduction of hot flashes, osteoporosis, urogenital symptoms and cholesterol. The smoking women should be recommended to use transdermal HRT that bypasses hepatic metabolism^[103].

Pharmacodynamic interactions

The pharmacodynamic drug interactions of cigarette smoking are mediated mainly by nicotine, which is a major active constituent of tobacco smoke. Nicotine comprises approximately 1.5% of tobacco weight in each cigarette^[104].

Combined hormonal contraceptives

Combined hormonal contraceptives (CHCs) contain both an estrogen and a progestin. CHCs are available as oral pills, injectables, patches and vaginal rings. The use of CHCs is associated with elevated risk of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial diseases

including MI and stroke^[105]. The women using CHCs containing levonorgestrel or norgestimate are at lowered risk of VTE compared to their peers using CHCs containing desogestrel, cyproterone, gestodene or drospirenone^[106]. The hypertensive women using CHCs may be at heightened risk of arterial diseases^[107].

Cigarette smoking is also associated with increased risk of arterial diseases and VTE^[108]. Smoking may cause VTE through nicotine-induced generation of platelet-dependent thrombin^[109] and smoking-related cardiovascular diseases^[110]. Tobacco smoking can induce the atherosclerotic changes and hypercoagulability resulting in adverse cardiovascular events^[111].

The risk of VTE^[112] and ischemic stroke and MI^[113] is elevated in women smokers using CHCs. Administration of CHCs in women older than 35 years and smoking more than 15 cigarettes a day, is contraindicated due to heightened risk of arterial adverse events^[114].

It has been estimated that approximately 27% of smoking women of reproductive age in the United States, use oral contraceptives concurrently^[115]. The women smokers using CHCs should be advised to quit smoking or to use progestin-only pills or other contraceptive methods.

Inhaled corticosteroids

Nicotine content of cigarette smoke can induce small airway inflammation^[116] and decrease the sensitivity of inhaled corticosteroids in asthmatic patients^[117,118]. The patients with chronic asthma and with the habit of regular smoking should be advised to quit smoking or be recommended to use antiasthmatic drugs other than inhaled corticosteroids^[119].

Benzodiazepines

Benzodiazepines (BZDs) are effective sedative, hypnotic and anxiolytic drugs and they include alprazolam, chlordiazepoxide, diazepam, lorazepam, temazepam, triazolam, and oxazepam^[120]. Nicotine induces the release of various neurotransmitters including acetylcholine, dopamine, serotonin, glutamate, and others through the binding to presynaptic nicotinic acetylcholine receptors (nAChRs) in the brain^[121].

Attenuated sedation has been observed in patients taking BZDs and smoking concurrently^[122]. Excessive central nervous system depression may occur when the patients stop smoking while taking BZDs.

Opioids

Opioids are the drugs used to treat moderate to severe pain and they act on opioid receptors. Smoking is associated with hyperalgesia due to desensitization of nAChR^[123] and it was noticed that the pain relief provided by opioid analgesics was less in smokers^[124].

The smokers needed to be administered with higher doses of morphine, pethidine (meperidine) and propoxyphene^[125] and the smokers requiring opioid analgesics should be advised to quit smoking^[126].

Antihypertensives

Nicotine content of cigarette smoke increases the sympathetic activity and rises the blood pressure acutely^[127] and it was reported that the blood pressure elevated persistently due to heavy smoking^[128]. Cigarette smoking is associated with higher arterial stiffness leading to cardiovascular diseases^[129,130]. Pulse wave velocity (PWV) helps to measure the arterial stiffness and the stiffer arteries have higher values of PWV^[131]. The beneficial effects of amlodipine on PWV was delayed by long-term cigarette smoking^[132].

Antihyperlipidemics

Smoking increases the risk of vascular diseases through various mechanisms including elevated levels of oxidized low-density lipoprotein, triglycerides (TG), packed cell volume (PCV) and fibrinogen, reduced high-density lipoprotein (HDL) levels, increased carotid artery intima-media thickness (IMT), enhanced arterial stiffness, increased insulin resistance and intensified endothelial damage. It has been reported that smoking decreased the beneficial effects of statins on the reduction of morbidity and mortality associated with ischemic heart disease^[133].

Alcohol

Alcohol use in smokers can increase the smoking satisfaction, calmness, etc. of rewarding effects of nicotine^[134]. The alcoholics tend to be heavy smokers and the smokers seem to be heavy alcohol drinkers^[135,136].

CONCLUSION

Tobacco smoking is very common around the globe and most of the smokers are living in LMICs. Tobacco smoking including SHS and third hand smoke is associated with various health hazards. Tobacco smoke contains many chemicals including PAHs which involves in majority of pharmacokinetic interactions of smoking. PAHs of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1.

The smokers may need higher doses of drugs such as clozapine, olanzapine, haloperidol, chlorpromazine, fluvoxamine, duloxetine, mirtazapine, imipramine, theophylline, aminophylline, caffeine, riociguat, erlotinib, tacrine, warfarin, propranolol, Ropinirole, mexiletine, Frovatriptan, zolmitriptan, alosetron, flutamide, melatonin, Ramelteon, Tasimelteon, Rasagiline, Tizanidine, triamterene, ropivacaine, methadone and oral estrogens (Hormonal replacement therapy) due to enhanced CYP1A-mediated metabolism and upon smoking cessation they need to be monitored for toxicity of drugs and the dosage adjustments to be done if needed.

Smoking can also interact pharmacodynamically with the drugs including CHCs, inhaled corticosteroids, BZDs, opioids, antihypertensives, antihyperlipidemics and alcohol. The clinicians should be aware of the drugs affected by smoking, to prevent adverse effects especially at the time of smoking cessation.

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**REVIEW**

- 26 Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases

Chandra N, Srivastava A, Kumar S

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Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases

Niharika Chandra, Ankita Srivastava, Sunil Kumar

ORCID number: Niharika Chandra (0000-0002-0931-5231); Ankita Srivastava (0000-0002-4054-8391); Sunil Kumar (0000-0001-7632-7252).

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Niharika Chandra, Faculty of Biotechnology, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Uttar Pradesh 225003, India

Ankita Srivastava, Sunil Kumar, Faculty of Bio-Sciences, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Uttar Pradesh 225003, India

Corresponding author: Sunil Kumar, PhD, Associate Professor, Faculty of Bio-Sciences, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Lucknow-Deva Road, Uttar Pradesh 225003, India. sunil.bio@srmu.ac.in
Telephone: +91-73-79893670

Abstract

Inflammatory bowel disease (IBD) has been a worldwide health problem. It is characterized by severe intestinal inflammation due to immune responses against the gut microbes in genetically susceptible individuals. The understanding of gut microbiota for its composition and complex interaction in normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics studies. The alteration of intestinal microbiota is the key determinant in the degree of inflammation caused and the prolonged course of disease. The relationship between luminal gut bacteria and innate immunity is also of prime significance. Such developments have further led to the search of specific (including bacteria and fungi) as a causative agent of IBD. Although detailed research has been done for the role of gut microbiota in IBD, molecular mechanisms and related gene expression are still not well understood in this disease, which hampers the generation of effective therapeutic agents for IBD. This paper assessed various factors contributing to IBD, genetic dysbiosis and pathogenic influence in the gut microbiota, interactions such as microbiome-host immune system interaction and microbe-microbe interactions involved in IBD, currently available IBD therapies, followed by a detailed review on bacterial infections that might be involved in IBD, globally and specifically in India.

Key words: Ulcerative colitis; Crohn's disease; Inflammatory bowel disease; Gut microbiota; Lactic acid bacteria

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Core tip: Ulcerative colitis and Crohn's disease are two clinical forms of inflammatory bowel disease (IBD) causing recurring diarrhea, abdominal bleeding, pain and inflammation. Scientific evidence clearly indicated the role of heredity in IBD, but an

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accurate cause of IBD is still unclear. However, complex interactions between genes, environmental factors and the immune system could be one of the leading causes in IBD. Gut microbiome is a key link between these factors and progression of IBD. This article reviews all contributing factors and pathogenic association in IBD. Identifying such microbial causes of the onset of IBD can help researchers to develop effective treatment strategies.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a common gastrointestinal disorder whose pathophysiology is still not completely understood due to its complex and multifactorial nature. It is generally characterized by abdominal pain and recurring diarrhea. It occurs in genetically vulnerable populations or individuals due to inappropriate and intensified immune response to commensal bacteria, which leads to intestinal inflammation^[1,2]. The two main clinical forms of IBD according to their location and nature of histological modifications/damage caused in the gastrointestinal wall are ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to mucosal surfaces of the colon, cecum and rectum. Several microbes such as *Salmonella spp.*, *Shigella spp.*, *Fusobacterium spp.*, and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC^[1-4]. CD exhibits transmural inflammation and the mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual^[5,6]. The most predominant bacterial species found in CD was *Bacteroides spp.*, which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of *Listeria monocytogenes* and adherent-invasive *E. coli* (AIEC) has been determined in CD^[5,6]. Both UC and CD cause diarrhea with or without bleeding and patients display a weakened tolerance to antigens present in the intestines^[1]. Its occurrence is similar in both sexes (men and women), and most cases are recorded in young adults^[6,7].

Depending upon the type of microbes, several unfriendly and mutuality interactions occur between the residing gut microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating. Also, formation of biofilms protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics^[5,8]. The residing microbes also regulate their gene expression in response to changing microbial cell population and its concentration through a cell-cell communication known as quorum sensing^[9].

UC

UC is the chronic and recurring IBD in which severe inflammation and immune responses (T helper cell and production of cytokines) are generated in the intestinal mucosa. The initiation site for ulcers is distal large intestine, and eventually the inflammation moves towards the proximal bowel. UC can severely disturb the quality of life, and if oral medicines are not effective, surgical removal of parts of ulcer affected intestines is obligatory. Several microbes such as *Shigella spp.*, *Fusobacterium spp.* and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC^[2-4].

CD

CD exhibits transmural inflammation and epithelioid granulomas in the gut tissues with T-helper cell (Th1) responses and elevated levels of interferon gamma. The mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual^[5,6]. Higher levels of antibody IgG is a characteristic of CD patients. The most predominant bacterial species found was *Bacteroides spp.*, which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of AIEC has been determined in CD^[5,6].

Rural populations are less susceptible to IBD. Environmental factors such as poor sanitation, decreased use of antibiotics, rural environment, consumption of whole unrefined food, *etc* decrease the risk of IBD. That is increased exposure to microbes or infection will lead to low susceptibility for IBD infection. Also, the mucosal immunity in intestines is changed during IBD. UC and CD patients tend to secrete more antibodies (IgG and IgA) against the commensal intestinal microflora and damage their intestinal mucosa^[10,11]. Thus, the pathogenesis of IBD is partly understood, and it has also been discovered that multiple factors are associated with IBD such as genetic vulnerability, environmental factors, host-commensal/pathogenic microbe interaction and disturbed mucosal immune responses^[12-14].

ENVIRONMENTAL FACTORS CONTRIBUTING TO IBD

The maximum occurrence of IBD has been reported in Northern Europe and North America, whereas it is rare amongst Asians and Africans. Incidences of IBD vary depending on race, and its prevalence increases in regions with industrialization. According to the hygiene hypothesis, the autoimmune and inflammatory responses in the body occur due to the absence or low exposure to pathogens in childhood/infancy due to rigorous sanitation practices.

The effect of smoking was guarding against UC and aggravating for CD. That is smoking may improve one's condition during UC, but CD patients may suffer with a declined quality of life. Other factors, such as domestic hygiene, prenatal events, oral contraceptives, microbial agents and refined sugar consumption require further evaluation to confirm their involvement in IBD and to describe their strength^[15-17]. Another accepted factor to increase IBD inflammation and cause relapse of the disease is psychological stress. Any sort of depression, adverse life situations or chronic stress can deteriorate the course of disease^[18,19]. Several clinical studies suggest that IBD is not a psychosomatic disease, but stressful life events and depression are associated with high risk of relapse and increased pathogenesis of IBD^[20,21].

GENETIC SUSCEPTIBILITY IN IBD

Heterogeneous geographical distribution and occurrence of ancestral forms of IBD as well as monozygotic twin studies strongly support the genetic component of IBD. High risk in patients having family members with IBD, relatively high risk of siblings acquiring the disease and high concordance rate of monozygotic twins than dizygotic twins of being affected by IBD further strengthen the hypothesis. Therefore, genetic makeup plays an important role in both forms of IBD. Also, several susceptibility genes have been reported. Autophagy genes such as ATG16L1, IRGM and Card15/NOD-2 have been reported to be associated with CD for innate immunity responses. Other candidate genes involved in UC are HERC2, STAT3 and PTPN2^[22,23]. Several other susceptible genes such as IL23R, IBD5, NKX2-3, BSN, IL12B and CCNY have been found to be associated with both UC and CD. **Table 1** lists some of the genes and their respective roles in IBD. Mutations in these particular genes can lead to abnormal immune response generation in the gut mucosa and adversely affect healthy microbial population in terms of composition and concentration.

COMPLEXITY OF GUT MICROBIOTA

The complex anaerobic environment of the gut is home to several microbial communities including bacteria, archaea and fungi. This microbial diversity in the gut has been studied by the culture independent 16S rRNA studies. These studies indicate that the gut is mainly inhabited by Gram-positive *Firmicutes* and Gram-negative *Bacteroidetes*, while *Actinomycetes*, methanogens and fungi are present in lower quantities^[24]. Most *Firmicutes* were identified as clostridia and are butyrate-producing bacteria. Several *Proteobacteria* and *Actinomycetes* were also identified out of which *Bifidobacteria* (subgroup of *Actinomycetes*), which has health promoting utilities was

Table 1 Susceptible chromosomal loci for inflammatory bowel disease

No.	Related disease	Gene(s)	Role(s) in inflammation	Ref.
1	UC + CD	NOD2/CARD15, CD19, CD11, IL4R	Detection of cytosolic bacterial components	[105]
2	UC + CD	IL23R, PTGER4	Generation and maintenance of Th17 cells; prostaglandins signaling	[23,106]
3	CD	IRGM, IL12B	Autophagy	[22,23]
4	CD	STAT3, ORMDL3	Development of T cell response	[22,23]
5	CD	IL3, IL4, IL5 and IL13, OCTN1, OCTN2, CSF2, SLC22A5	Mucosal barrier function, cytokines production, Regulation of inflammation	[106]
6	UC + CD	MST1, BSN, GNAI2	Regulation of expression of proinflammatory mediators	[105]

CD: Crohn's disease; UC: Ulcerative colitis; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; CARD15: Caspase recruitment domain-containing protein 15; CD19: Cluster of differentiation 19; IL4R: Interleukin 4 receptor; IL23R: Interleukin 23 receptor; PTGER4: Prostaglandin E receptor 4; IRGM: Immunity related GTPase M; IL12B: Interleukin 12B; STAT3: Signal transducer and activator of transcription 3; ORMDL3: Orosomucoid like 3; OCTN1: Organic cation transporter, novel, type 1; CSF2: Colony stimulating factor 2; SLC22A5: Solute carrier family 22 member 5; MST1: Macrophage stimulating 1; BSN: Bassoon (presynaptic cytomatrix protein); GNAI2: G protein subunit alpha I2.

found to be 5% of the microbiota. Archaeal diversity consists of *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*. Eukaryotic microbes in the human gut consist of *Blastocystis* sp., (uni- and multicellular protists) and several fungi belonging to *Ascomycetes* (53.5%) or *Basidiomycetes* (46.5%) with the majority belonging to the genera *Candida albicans*, *C. glabrata* (6%), *Penicillium italicum*, *P. glabrum*, *P. sacculum*, *P. verruculosum* (61.5%), *Saccharomyces cerevisiae*, *S. cariocanus* and *S. bayanus* (24.1%)^[24-26].

PATHOGENIC INFLUENCE OF GUT MICROBIOTA IN IBD

Several studies aiming to distinguish residing microbes in a healthy gut and an IBD gut revealed an overall decline in bacterial diversity in IBD patients. Further, a decrease in methanogen diversity and an increase in fungal diversity were noted in the guts of IBD patients^[25,26]. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities did not vary over the healthy gut tissues.

Different studies have also reported the presence of pathogenic microbes in the gastrointestinal tract of IBD patients. *Saccharomyces cerevisiae*, *Candida albicans*, *Listeria monocytogenes*, *Mycobacterium avium* subsp. paratuberculosis, *Chlamydia pneumonia* and AIEC have been reported as the potentially infectious microbes in the spread of CD. In CD, *Bacteroides*, *Peptostreptococcus* and *Eubacteria* are increased, whereas *Bifidobacteria* numbers are considerably reduced. Moreover, in UC the presence of facultative anaerobic bacteria is amplified. Table 2 lists the infectious agents (viral, bacterial, fungal and parasitic agents) that have been suspected in IBD etiology. *E. coli* has been reported to induce the release of cytokines in the inflamed IBD gut. AIEC, which is a facultative pathogen, has been reported to cause CD in genetically susceptible hosts^[27-29]. Even though these studies have shown relation between pathogens and IBD, specific pathogenic microbes responsible for CD or UC is still contentious.

GENETIC DYSBIOSIS IN IBD

IBD may not be caused by any specific microbial infection; instead it occurs due to a change in the overall residing microbes in the gut (intestinal microbe biofilms). It may also be caused by misrecognition of normal, commensal microbes as foreign leading to immune responses and inflammation. This change in intestinal microbiota (in terms of species and their concentration) or misrecognition by the body is termed genetic dysbiosis^[30,31]. This ever-changing gut microbiota can modify the expression of certain genes that are involved in various activities in the intestines. Further, it can cause inflammation and disease in genetically susceptible individuals who have mutations or polymorphism in genes involved in immune responses (as described in previous

Table 2 Suspected pathogenic microorganism in tissue of patients with inflammatory bowel disease

Bacteria	Virus	Fungi
<i>Campylobacter</i> spp.	Adenovirus	<i>Saccharomyces cerevisiae</i>
<i>Escherichia coli</i>	Cytomegalovirus	<i>Candida albicans</i>
<i>Helicobacter</i> spp.	Coronavirus	
<i>Legionella</i> spp.	Rotavirus	
<i>Mycobacterium</i> spp.	Measles virus	
<i>Pseudomonas</i> spp.	Paramyxovirus	
<i>Shigella</i> spp.	Epstein-Barr virus	
<i>Yersinia</i> spp.		Parasite
<i>Bacteroides vulgatus</i>		<i>Borrelia</i> spp.
<i>Listeria monocytogenes</i>		<i>Treponema</i> spp.
<i>Staphylococcus</i> spp.		
<i>Streptococcus</i> spp.		
<i>Enterococcus</i>		
Adherent-Invasive <i>E. coli</i>		
<i>Chlamydia</i> spp. (<i>Chlamydia trachomatis</i>)		

spp.: Species.

sections)^[30,31]. **Figure 1** represents how genetic dysbiosis can lead to diseases.

INTESTINAL MUCOSAL BARRIER FUNCTION IN IBD

The intestinal mucosal barrier consists of two layers of mucus (inner and outer), which are associated with antimicrobial factors. Under this mucus layer are the gut epithelial cells that are joined together by a network of connecting proteins called tight junctions. Hence, this intestinal mucosal barrier splits the luminal components (food particles, microbes, *etc.*) from the immune system components (innate and adaptive immunity) (**Figure 2**)^[32].

MICROBIOME-HOST IMMUNE SYSTEM INTERACTION IN IBD

Under normal conditions the microbiota does not interact with the epithelial cells, other than the controlled interaction in the Peyer's patches. Under the condition of disturbed microbiota composition or genetic dysbiosis, as is the case with IBD, this mucosal barrier is interrupted, and the interaction between the microbiota and immune system components occurs, which leads to generation of a heightened immune response and inflammation as shown in **Figure 2**.

In IBD, the mucus layer is permeable and defective due to improper secretion of mucus components by goblet cells (decreased mucin, antimicrobial factors, glycosylation products, *etc.*). In the case of UC, the goblet cells are depleted in the epithelium, and the mucus layer formed is very thin. Also, the tight junction protein network becomes increasingly penetrable in IBD, which further increases the interaction between immune and luminal components. Such changes are a result of environmental factors and genetic dysbiosis as discussed earlier^[33,34].

Various studies have shown that microorganisms that pass the mucus layer and invade the epithelial cells, activate various components of the immune system comprising innate immune responses, adaptive immune responses and autophagy^[35,36]. According to Parkes, CD is linked to mutations in autophagy genes such as nucleotide oligomerization domain 2 and ATG16L1. Intracellular pathogens have also been observed to form autophagic vacuoles to prevent interaction with immune components and remain protected^[37].

Microorganisms that pass through the damaged tight junctions mesh and reach the lower surface of epithelial cells are recognized by the pattern recognition molecules similar to toll-like receptors present there. This interaction then activates the innate

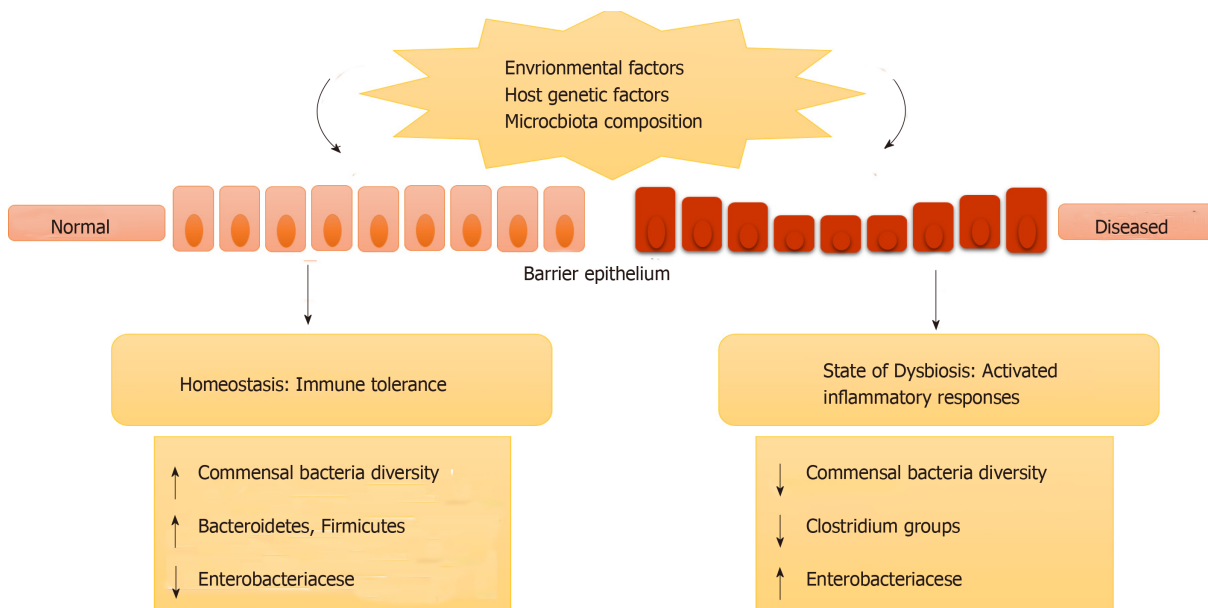


Figure 1 Pathway for genetic dysbiosis.

immune responses (including phagocytic cells, natural killer cells, dendritic cells, inflammation-related proteins, cytokines and antimicrobial peptides such as defensins and cathelicidins) and adaptive immune response including several cytokine profiles^[38,39]. Fernandes *et al*^[40] reported that in IBD, the expression of regulatory molecules of immune system and toll-like receptors is different from that in a healthy tissue.

MICROBE–MICROBE INTERACTIONS IN IBD

Other than interaction with the host cells, the survival and activity of gut microbiota also depends upon their interaction with the other surrounding microbes. These interactions can be unfriendly or mutualistic, which primarily depends upon the type of microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating (Figure 3).

Combatting

Gut bacteria combat other microbes by production of antimicrobial peptides (AMP) and specialized secretions. Bacteriocins, colicins and microcins are some AMP that inhibits other microbial invading species without harming the eukaryotic gut cells. Bacteriocins are produced by Gram-positive bacteria, and they fight against other microbes by pore formation in their cell wall. Gram-negative bacteria produce colicins and microcins, which kill other microbes by a variety of strategies such as nuclease activity, inhibition of RNA polymerase, intervention cell wall synthesis and pore formation^[41,42]. These bacterial AMPs under the effect of environmental factors control surrounding microbiota composition and concentration.

Other mechanisms of combatting surrounding microbes are contact dependent growth inhibition systems and type VI secretion systems. In contact dependent growth inhibition system, the C terminal end of CdiA protein move in on the target cell and kill it by nuclease activity. Type VI secretion system cells inject toxins in Gram-negative bacteria and eukaryotic cells to combat bacterial competition and cause pathogenesis, respectively^[41,42].

Competing

One of the essential parameters that governs colonization of microbes and dysbiosis in gut is the competition for carbohydrates. Other than carbohydrates, bacteria also compete for phosphorus, nitrogen, vitamins, trace elements and other vital cofactors. Bacteria encode a variety of transporters for smooth uptake of vitamins and essential cofactors^[43,44]. Some bacteria interfere with the uptake of trace elements by other bacteria by secretion of some inhibitors or AMP. For instance, a study by Raffatellu *et al*^[45] showed that *Salmonella typhimurium* produced lipocalin-2 to inhibit iron uptake by surrounding microbes.

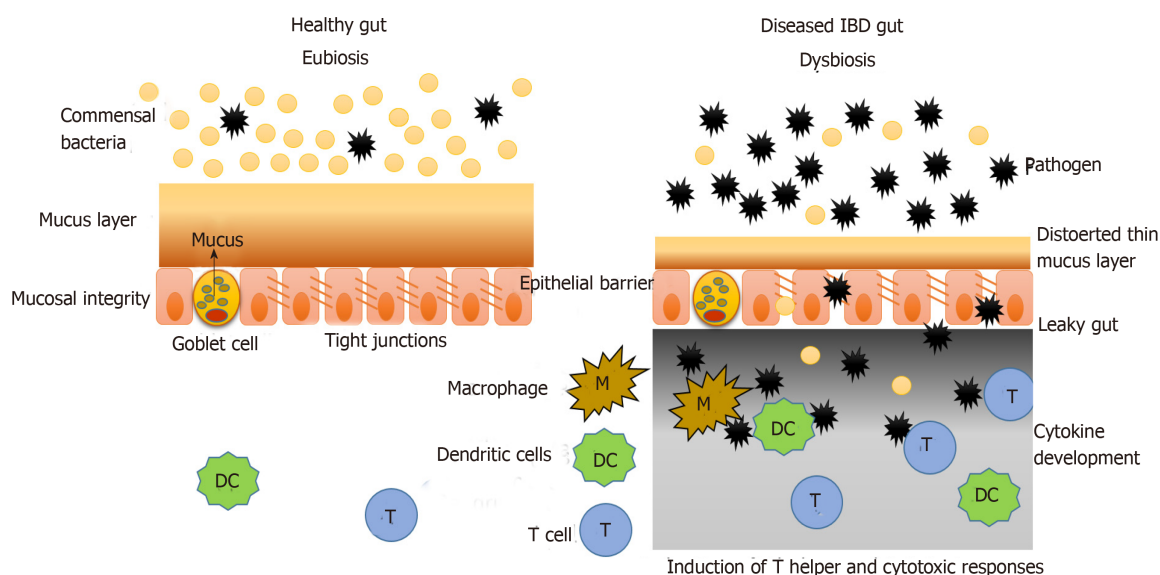


Figure 2 Mechanism of inflammatory bowel disease.

Cooperating and communicating

Even after such limiting conditions and competition for food, gut bacteria also communicate and live in cooperation and share by-products. One of the methods of such cooperation is horizontal gene transfer. Horizontal gene transfer is responsible for secretome molecules, which is the most common method to help in production of certain molecules for communal use. For instance, chelators of iron (siderophores), which help in absorption of iron from the surrounding, can be used by any bacteria in the surrounding. In this way, horizontal gene transfer of such genes and public use of these secretions helps the bacterial population to live in cooperation in the gut^[46,47].

Formation of biofilms also protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. It prevents the loss of useful secretions and nutrients from a population of microbes living in cooperation with other surrounding microbes. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics^[5,8].

Many cooperative/group behaviors in the gut are governed by the cell-to-cell communication called quorum sensing (QS). The signaling molecules are released in the environment and regulate gene expression in the surrounding communities. QS governs several mechanisms important to survival such as biofilm formation, antibiotic production and expression and release of secretions like type VI secretion systems. Although QS has been known in *Lactobacillus* species and probiotics, its role in human gut commensal bacteria and pathogens is still not understood well. Further studies are necessary for understanding the microbial communication in both homeostasis and IBD conditions^[48-50].

Quorum sensing

QS occurs by the production and release of extracellular chemical signal molecules called autoinducers by bacteria that are subsequently detected by other bacteria. When a particular threshold concentration of autoinducers is reached, the gene expression is altered in all the bacterial cells residing there. This alteration in gene expression is associated with the variations in cell population density^[9]. Several physiological activities such as biofilm formation, virulence, competence, symbiosis, conjugation, antibiotic production, sporulation and motility are controlled by QS communications in bacteria. This communication through autoinducers can take place both within and amongst the bacterial species. Acylated homoserine lactones are produced as autoinducers in Gram-negative bacteria, while Gram-positive bacteria release oligopeptides for communication^[9,51].

Gram-negative bacteria *V. fischeri* demonstrated LuxI/LuxR-type QS. LuxI-like proteins synthesized a particular acylated homoserine lactone signaling molecule, which is an autoinducer. When these homoserine lactone signaling molecules reach a threshold concentration, LuxR-like proteins bind to them and stimulate particular gene transcription^[52]. Several other Gram-negative bacteria, including those involved

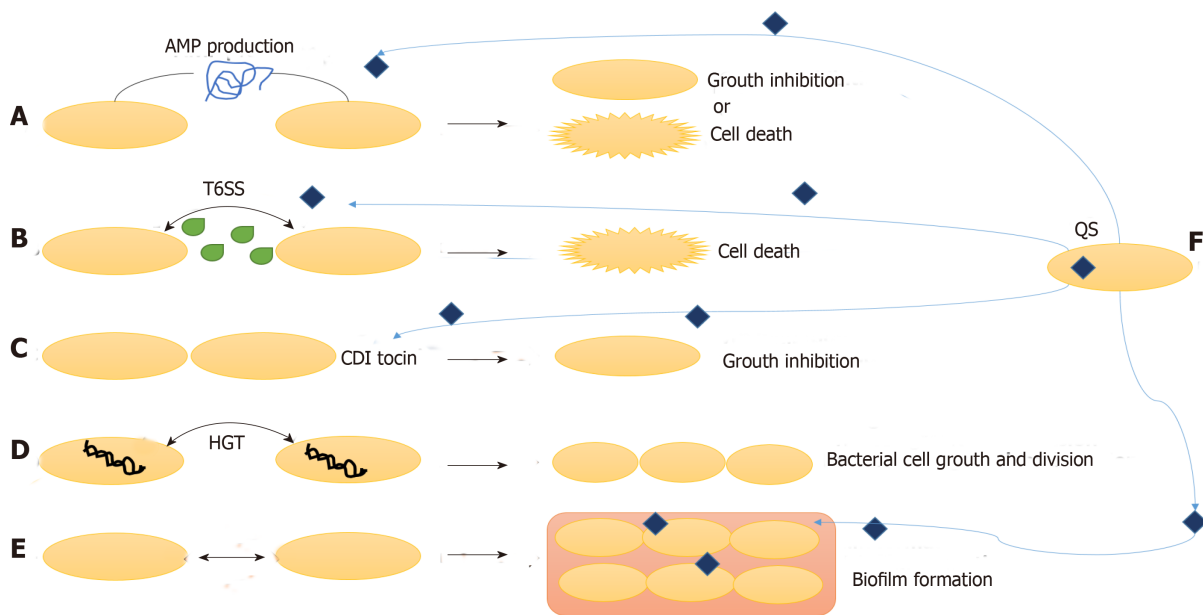


Figure 3 Various communication mechanisms used by bacteria (combatting: A-C; cooperating: D-F). A: Antimicrobial peptides; B: Type 6 secretion system; C: Contact-dependent growth inhibition systems; D: Horizontal gene transfer; E: Formation of a protective biofilm; F: Quorum sensing^[39].

in pathogenesis of IBD regulate gene expression through homologous LuxI/LuxR-type circuit. For instance, in *P. aeruginosa*, LasI/LasR-RhlI/RhlR virulence system circuit regulates QS. Homoserine lactone signaling autoinducers N-(3-oxododecanoyl)-homoserine lactone and N-(butyryl)-homoserine lactone are produced by the action of LasI and RhlI autoinducers. Expression on several virulence factors (lasB, lecA and aprA) in *P. aeruginosa* is controlled by this circuit^[53,54].

Gram-positive bacteria also show QS mediated regulation by secreting peptides as autoinducers. An example of this is *Staphylococcus aureus* AgrC/AgrA virulence system. An RNA molecule named RNAIII regulates biofilm formation and pathogenicity in *S. aureus*. The *agrBDCA* operon regulates the levels of RNAIII. Function of RNAIII is to express several virulence factors in *S. aureus*^[55,56].

In a recent study by Goliska *et al*^[57], pathogenicity of enterococci (*Enterococcus faecalis*) in IBD was studied. The expression of several genes encoding the virulence factors (gelatinase, extracellular surface protein, cytolysin and hyaluronidase) was studied in IBD patients and control groups. The strains with these virulence genes were also found to have QS genes *fsrA-C* that regulates the expression of these virulence factors.

IBD THERAPIES

Any effective therapeutic strategy to treat IBD should be able to treat all its pathophysiological constituents including inflammation, dysbiosis and leaky gut. The currently available medical treatments of IBD involve three approaches: immune-based therapies, microbiota-based therapies and barrier function-based therapies. Even after these advanced approaches, some patients still require surgical removal of severely affected portions of GI tract^[58].

Immune-based therapies

Immune-based therapies directly modulate the immune system to avoid further destruction of commensal microbiota and the gut tissues to relieve inflammation. Furthermore, these therapies also indirectly modulate the mucosal barrier function and the microbiota^[58,59]. Immune-based therapy medication includes immunomodulators (*e.g.*, methotrexate, azathioprine), aminosalicylates, corticosteroids, integrin inhibitors and antitumor necrosis factor agents. Several other biologics are being developed to downregulate inflammatory cytokines and their receptors along with rebuilding healthy barrier function^[59]. Mesalamine and other salicylates are known to modulate the intestinal microbial composition and decrease microbial adherence and biofilm formation in the gut^[39,58].

Microbiota-based therapies

Microbiota-based therapies are based upon use of antibiotics, probiotics, fecal microbiota transplantation and alteration in diet.

Antibiotics: Antibiotics have been found most effective in CD and only of little use in UC, where it is sometimes used to treat children. Antibiotics such as rifaximin, metronidazole, ciprofloxacin and antimycobacterial agents are being used. These antibiotics decrease the concentration of some pathogens and increase the content of healthy microbiota including *Bifidobacteria* and *F. prausnitzii*. Indiscriminate use of antibiotics can lead to severe side effects such as reduction in microbial biodiversity in gut and developing resistance in microbes^[60,61].

Probiotics: Probiotics can be defined as the living organism (specific bacterial strains together) that when ingested provides health benefits and protective regulatory activities in the body. Commonly the content of yogurts such as *Lactobacilli*, *Bifidobacteria* and *Streptococci* play the role of probiotics. Probiotics have more efficiently been used in UC and are less effective for CD patients. The most extensively used probiotics for IBD are VSL#3 and *E. Coli* Nissle 1917. VSL#3 are a combination of eight diverse bacterial strains (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*). These bacteria stimulate the growth of anti-inflammatory bacteria and prevent the growth of pathogenic microbes^[62,63].

The use of lactic acid bacteria, which includes *Lactobacillus*, as probiotics for treatment and prevention of IBD has been proposed in several studies. They are Gram-positive bacteria that normally reside in anaerobic conditions but are facultative aerobes^[64,65]. They provide probiotic action by production of bacteriocins, hydrogen peroxide, lactic acid and by forming dense biofilms on gut epithelium, which block all the adhesion sites for attachment of pathogens^[65]. *Lactobacillus* species such as *L. casei*, *L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *L. fermentum*, *L. amylovorus* and *L. delbrueckii*, etc have been extensively studied for probiotic action against *H. pylori*, *Salmonella*, *E. coli*, *Clostridium difficile*, *Yersinia enterocolitica* and *Listeria monocytogenes*, etc^[65,66]. The microbial interactions amongst themselves and with other commensal/pathogenic microbes in the biofilms formed in the gut are regulated by the *luxS* gene QS mechanisms. Several other proteins that are involved in biofilm formation in different *Lactobacillus* strains consist of collagen-binding protein, biofilm associated proteins, glycosyl-transferases and mucus-binding protein^[66,67]. Most of the *Lactobacillus* species are bacteriocin producing. A specific class of bacteriocin, called plantaricins are produced by some species such as *L. plantarum* and *L. fermentum*. The plantaricin genes which can be identified in *Lactobacillus* are *plnA*, *plnB*, *plnC*, *plnD*, *plnEF*, *plnI*, *plnJ*, *plnK*, *plnG*, *plnN* and plantaricin structural genes^[68,69].

Fecal microbiota transplantation: This strategy of re-establishing healthy microbiota and treating IBD involves ingestion of healthy donor stool by an ill individual. This has been extensively used with mixed and moderate results in IBD patients. Repetitive infusions are required for sustained results. Keeping in view the chance of transmitting infectious microbes, recent studies suggest the use of artificial stool with limited risk of such infections^[70,71].

Alteration in diet: A balanced, high fiber, healthy diet with vegetables, fruits and grains is recommended for IBD patients. Diets with high protein content, excessive red meat and alcohol abuse are discouraged in IBD as it may aggravate or relapse the inflammation. Specific carbohydrate diets that eliminates milk, grains and sugar from the diet has been found effective in some cases of IBD showing an improvement in microbiota diversity^[72,73].

Barrier function-based therapies

This therapy is evolving as the most effective and future approach for treating IBD. If the mucus layer in the gut epithelia is restored, then eventually the immune responses and inflammation can be controlled as well as microbiota diversity can flourish.

Establishing healthy microbiota and inhibition of TNF α and other inflammatory cytokines have recorded an enhanced barrier function in case of IBD. Amino acid, L-glutamine supplements and natural ingredients such as curcumin have been shown to restore tight junctions and hence can be used in treating IBD. Delayed released drugs such as phosphatidylcholine are also being examined extensively as a cure for IBD^[39,74-76].

BACTERIAL INFECTION IN IBD

Prominence worldwide

A number of studies with the aim to distinguish between residing microbes in a healthy patient and an IBD patient revealed an overall decline in bacterial diversity in the gut of patients with IBD^[25,26]. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities may not vary over the healthy gut tissues. Different studies have also reported the presence of pathogenic microbes in gastrointestinal tracts of IBD patients.

Ma *et al*^[77] studied the occurrence of *Campylobacter concisus* in CD patients colonic biopsy samples and concluded there may be potential involvement of *C. concisus* in IBD. In another study by Arora *et al*^[78] the risk of *C. jejuni* infection in UC was established.

Similarly, the presence of several virulence factors such as hyaluronidase, cytolysin and extracellular surface protein in *Enterococcus* strains isolated from colon tissue samples of children with IBD was observed^[57].

There are several studies that link *Helicobacter pylori* biofilms with gastrointestinal diseases, but it still remains debatable. Mice have developed IBD symptoms in the presence of abnormal immune response and *H. pylori* infection. No symptoms appeared in germfree conditions that establish single pathogen infection^[79]. Halme *et al*^[80] and Luther *et al*^[81] observed contradictory results and demonstrated a protective or inverse relation of *Helicobacter* towards IBD.

Furthermore, a study by Saebo *et al*^[82] concluded that infection of *Yersinia enterocolitica* was an activator for IBD. Similarly, Ruckdeschel *et al*^[83] analyzed the impact of virulence factors (such as cytotoxin, invasin and adhesin) of *Y. enterocolitica* against the action of polymorphonuclear leukocytes.

As far as the role of *Listeria monocytogenes* in IBD is concerned, studies revealed uncertain outcomes. *L. monocytogenes* was found proliferating at a higher rate in the colon of patients with IBD than in healthy controls^[84]. *Listeria* forms resistant biofilms on several surfaces including synthetic as well as gut epithelium. The biofilm formation is regulated by QS autoinducer 2 genes *luxS* and *pfs*. Chen *et al*^[85] studied the presence of *L. monocytogenes* in gut biopsies of IBD patients and controls in New Zealand and reported no direct role of *L. monocytogenes* in causing IBD. Another study by Huijsdens *et al*^[86] also reported a similar result. However, Ooi *et al*^[87] found *L. monocytogenes* responsible for causing mucosal inflammation in healthy individuals. Another recent study by Miranda-Bautista *et al*^[88] confirmed the presence of *L. monocytogenes* in patients of CD and concluded that IBD patients are at a serious risk of *L. monocytogenes* infection.

Numerous studies also demonstrate a relation between *Salmonella enterica* infection and IBD. It has been reported that IBD and *Salmonella* infection with coinciding medical and histological symptoms in an elderly woman. This case study reports that colitis may be associated with *Salmonella* infection^[89]. There are various other studies which elucidate the high risk of *S. enterica* infection in IBD^[90-92].

Even though these studies have shown a relationship between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable.

Prominence in India

The majority of IBD has been reported in northern Europe and North America, whereas it has been considered rare among Asians and Africans. But, in the past two decades cases of such western diseases have been witnessed in India, including UC and CD, and the number of affected individuals is rising alarmingly^[93]. Detailed studies regarding epidemiology and pathogenesis of IBD are lacking in developing countries like India due to neglected health care services, lack of reliable data collection and patient based studies^[93,94].

Several studies have reported the possible involvement of specific pathogens in IBD. Verma *et al*^[95] described that different sets of bacteria are responsible for pathogenesis of UC and CD. An increase in Gram-positive *Eubacterium* and *Peptostreptococcus* was reported in CD patients but not in UC patients, whereas *Campylobacter spp.* significantly increased in both CD and UC patients. A study by Patra *et al*^[96] reported the presence of various serogroups of adherent *Escherichia coli* in rectal biopsies of individuals and associated it with epithelial damage and CD. Banerjee *et al*^[97] reported occurrence of parasitic and viral infections (such as *Ankylostoma duodenale*, *Strongyloides stercoralis*, *Entamoeba histolytica*, etc) in UC patients by analysis of stool samples and rectal biopsies. Iyer *et al*^[98] investigated the relationship between intestinal infections (with *Clostridium difficile* and other parasites) and UC. They reported that the presence of such infections in UC patients deteriorated the condition and is associated with disease severity. Tripathi *et al*^[99] detected the presence of *Salmonella enterica* in the stool of 80% of UC patients and concluded an active infection of *Salmonella sp.* in IBD.

Another recent study examined the gut microbiota profile of vegetarian and non-

vegetarian healthy individuals and IBD individuals and colon carcinoma and reported that IBD and colon cancer patients had higher proportions of *Bacteroidetes* than *Firmicutes*^[100]. Several studies discuss the food-borne infection of *Listeria monocytogenes* in India. In another study^[101] established the expression of virulence gene regulator *prfA* in *L. monocytogenes* infecting mammalian host, which helps in formation of resistant biofilms and virulence. Expression of *prfA* was also studied in co-cultured biofilms with *B. subtilis*, which made *L. monocytogenes* less virulent in such biofilms.

Several studies have also been conducted regarding the anti-biofilm nature and probiotic properties of lactic acid bacteria against pathogenic bacteria. Kaur *et al*^[102] reported the action of *Lactobacillus spp.* against diarrhea causing *Vibrio cholerae*, which causes high mortality in developing countries like India. Another study examined the antimicrobial action of *Lactobacillus spp.* from curd and milk against several human infecting pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella enterica* serovar Typhi, *Bacillus cereus*, *Listeria monocytogenes* and *Shigella flexneri*[103]. Furthermore, in some studies it has been demonstrated the antimicrobial action of thirteen *Lactobacillus* isolates from the gastrointestinal track of broiler chicken against *Escherichia coli* and pathogenic fungi such as *Aspergillus niger*, *Aspergillus flavus*, *Penicillium expansum*, *Penicillium roqueforti* and *Candida albicans*, *etc*^[104-106]. The lactic acid bacteria showed effective inhibition against these pathogens.

CONCLUSION

The understanding of gut microbiota in terms of composition and its complex interaction in both normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics techniques. Even though several studies (as mentioned above) have shown relationships between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable. Also, detailed research has been done for gut microbiota and IBD, but the molecular basis of their virulence and biofilm formation still remains to be discovered. This has hampered the generation of effective therapeutic agents for IBD that would benefit a high percentage of the world population affected by the disease. Therefore, we need to understand the pathogenesis of IBD and develop strong treatment strategies against it.

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