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MINI REVIEW

Protective role of flavonoids quercetin and silymarin in the viral-associated inflammatory bowel disease: an updated review

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Abstract

Inflammatory bowel disease (IBD) is a chronic recurrent inflammation of the gastrointestinal tract (GIT). IBD patients are susceptible to various infections such as viral infections due to the long-term consumption of immunosuppressive drugs and biologics. The antiviral and IBD protective traits of flavonoids have not been entirely investigated. This study objective included an overview of the protective role of flavonoids quercetin and silymarin in viral-associated IBD. Several viral agents such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella zoster virus (VZV) and enteric viruses can be reactivated and thus develop or exacerbate the IBD conditions or eventually facilitate the disease remission. Flavonoids such as quercetin and silymarin are non-toxic and safe bioactive compounds with remarkable anti-oxidant, anti-inflammatory and anti-viral effects. Mechanisms of anti-inflammatory and antiviral effects of silymarin and quercetin mainly include immune modulation and inhibition of caspase enzymes, viral binding and replication, RNA synthesis, viral proteases and viral assembly. In the nutraceutical sector, natural flavonoids low bioavailability and solubility necessitate the application of delivery systems to enhance their efficacy. This review study provided an updated understanding of the protective role of quercetin and silymarin against viral-associated IBD.

Keywords Inflammatory bowel diseases · Viral infections · Quercetin · Silymarin · Antiviral traits

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Abbreviations

ARDS	Acute respiratory distress syndrome
GIT	Gastrointestinal tract
IBD	Inflammatory bowel disease
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV	Severe acute respiratory syndrome coronavirus
CD	Crohn's disease
UC	Ulcerative colitis
HBc	Hepatitis B core protein
HBs	Hepatitis B surface protein
HBs Ag	Hepatitis B surface antigen
Th	Helper T cell
Treg	Regulatory T cell
SCFAs	Short-chain fatty acids
TXNIP	Thioredoxin (TRX)-interacting protein
NLRP3	NOD-like receptor family pyrin domain-containing 3
SIRT1	Sirtuin (silent mating-type information regulation 2 homolog) 1

ASC	Apoptotic speck-like protein containing a caspase recruitment domain
IL	Interleukin
TNF- α	Tumor necrosis factor α
PGE-2	Prostaglandin E2
COX-2	Cyclooxygenase-2
iNOS	Inducible nitric oxide synthase
GPx	Glutathione peroxidase
CAT	Catalase
MDA	Malondialdehyde
GSH	Glutathione
SOD	Superoxide dismutase
PGA	Prostaglandin
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A

Introduction

Inflammatory bowel disease (IBD) includes the persistent/chronic or recurrent inflammation of the GIT epithelium mainly including ulcerative colitis (UC), involving the sigmoid and colon, and Crohn's disease (CD), involving the entire GIT (Song and Wu 2022). Another heterogeneous disease process has been identified and classified as IBD unclassified (IBDU) with periods of remission and exacerbation (Malik 2015). The disease mostly affects individuals aged 20–40 years and influences all living aspects posing a considerable socioeconomic burden (Burisch et al. 2023). The relapse and remission of IBD is a great concern among patients with a rate of 50–80% (Cohen et al. 2010). The chronic trend of the IBD needs long-term protection which in turn increases the costs. The supposed pathophysiological mechanism of the disease includes severe immune responses in the gut epithelium particularly among genetically predisposed individuals (Su et al. 2019; Pavel et al. 2021b). The IBD has four stages (emergence, acceleration in incidence, compounding prevalence, prevalence equilibrium) according to the developing conditions of societies worldwide (Molodecky and Kaplan 2010; Kaplan and Windsor 2021). Major etiological agents of IBD include genetic basis, aberrant immune responses and epigenetic factors (Sheehan et al. 2015; Dudzińska et al. 2018). Single-nucleotide polymorphisms (SNPs) and different expression levels of immune-responsive genes such as G protein-coupled receptor 183 (GPR183), IL23/Th1/Th17 pathway (IL23R, DLG5, JAK2, STAT3 and TYK2), predispose individuals to the IBD development (Fransen et al. 2014; Tillack et al. 2014; Dudzińska 2020; Ruiz et al. 2021).

The human gut microbiota plays a crucial role in GIT health through the regulation of inflammatory responses and hence control of the IBD pathophysiology (Wallace et al. 2014; Andreou et al. 2020; Kumari et al. 2022) (Figs. 1 and 2). Various conditions which disrupt the balance and diversity of gut microbiota (dysbiosis) and intestinal homeostasis lead to the growth of pathogens and the consequent initiation of systemic inflammation. Lifestyle, diet, antibiotic consumption, environmental factors and stress conditions include potential risk factors (Jostins et al. 2012; Sheehan et al. 2015; Statovci et al. 2017; Cui and Yuan 2018; Piovani et al. 2019; Andreou et al. 2020; Miri et al. 2022). The gut microbiota dysbiosis in the IBD can be translated into a decrease in *Suterella*, *Bacteroides* and *Saccharomyces cervisiae*, *Faecalibacterium prausnitzii*, *Roseburia* species, *Bifidobacterium* spp and Groups IV and XIVA of *Clostridium* (Rivière et al. 2016; Pavel et al. 2021a). Additionally, a related increase in *Caudovirales*, *Clavispora lusitaniae*, *Pasteurellaceae*, *Veillonellaceae*, *Fusobacterium* species, *Ruminococcus gnavusa, Proteobacteria* and adherent invasive *Escherichia coli* pathogens has been documented (Sokol et al. 2017). In this context, probiotics can be also of help. The protective role of probiotics includes inhibition of pro-inflammatory cytokines and interleukins release, Toll-like receptors (TLR)-mediated inflammation, regulation of T helper (Th) cells and increase in mucin genes expression (e Silva et al. 2020; Pavel et al. 2021a). In addition, probiotics mitigate the risk of hereditary IBD. *Lactobacillus* and *Bifidobacterium* species figure out between the major probiotics play key roles in GIT health, applied to heal IBD or UC complications (Pavel et al. 2021a; Miri et al. 2022). Figures 1 and 2 describe the variety of mechanisms by which the gut microbiota contribute to protect the mucosal barrier and to prevent epithelial inflammation.

It is worth mentioning that the toxicity and costs of chemotherapy are much higher than those of herbal medicines (HMs) bioactive compounds, both eliciting equal anti-inflammatory effects (Hess et al. 2016; Yajima et al. 2016; Assiry et al. 2022; Safarpour et al. 2022; Sun et al. 2022; Vazifeh et al. 2022). As secondary metabolites, flavonoids confer a myriad of health benefits such as antiviral, antimicrobial, anti-inflammatory, antioxidant, anticancer, antidiabetic and cardioprotective effects (Roy et al. 2022). In a review study, the antiviral effects of naringenin, rutin, quercetin, vitexin and apigenin were assessed. Their main mechanisms of action included viral protein modifications and inactivation of viral DNA/RNA polymerases, proteases and neuraminidase (Ninfali et al. 2020). The non-toxicity of flavonoids and antiviral effects of quercetin (inhibiting influenza A neuraminidase) and silymarin (against hepatitis C virus) have been demonstrated (Ferenci et al. 2008; Wu et al. 2015; Badshah et al. 2021a). Although numerous flavonoids have demonstrated anti-inflammatory and antiviral effects, the current study offered insights on the efficacy of quercetin (a flavanol) and silymarin (also flavo-lignane). Quercetin and silymarin (Fig. 3) flavonoids applied in various formulations have proved numerous health-related effects such as antioxidant, anti-inflammatory and antiviral properties, while

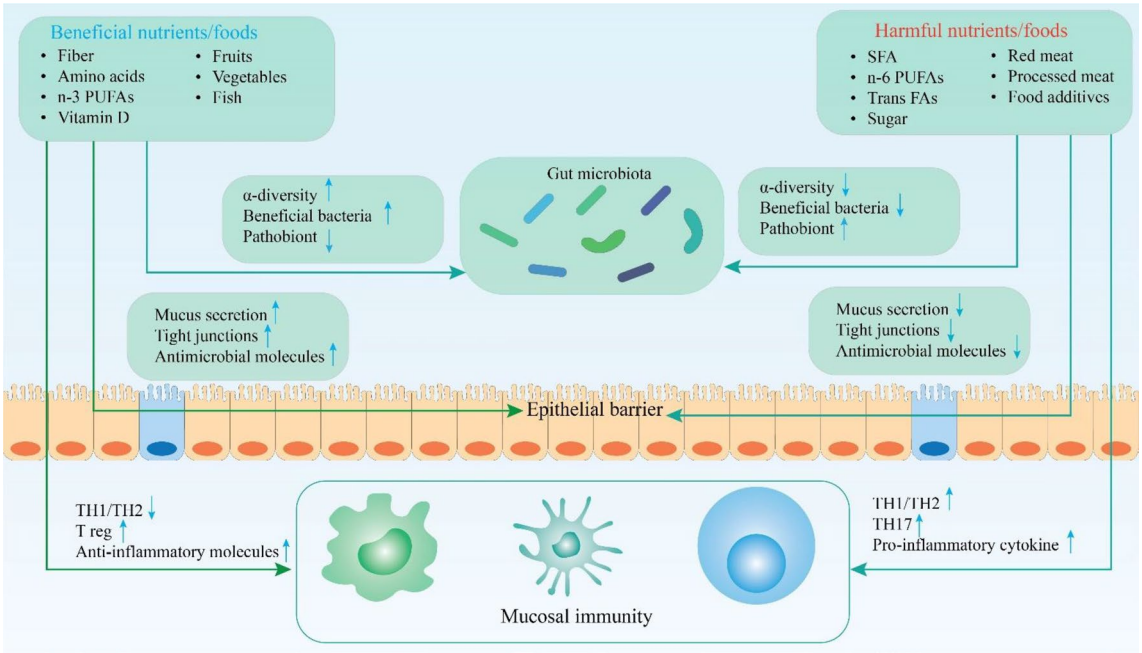


Fig. 1 The role of gut microbiota in GIT (gastrointestinal tract) health and IBD (inflammatory bowel disease) prevention; the consumption of vegetables and fruits, fiber, vitamins and n-3 PUFAs (polyunsaturated fatty acids) results in the gut microbiota prospering and proliferation exerting anti-inflammatory effects and offering the GIT protection. Additionally, these healthy foods directly regulate the Th1/Th2 cells and increase Treg and anti-inflammatory cytokines providing health conditions for the epithelial barrier. On the contrary, unhealthy foods such as SFAs, n-6 PUFAs, trans-FAs, sugar, red meat, processed meat and food additives decrease the microbial diversity and also beneficial bacteria. These conditions lead to the pathobionts population increase and subsequent development of epithelial inflammation (Jostins et al. 2012; Wallace et al. 2014; Cui and Yuan 2018; Andreou et al. 2020; Li et al. 2022; Liu et al. 2022). *PUFAs* polyunsaturated fatty acids, *TH1* T helper 1 or cytotoxic T cells, *TH2* T helper 2 cells, *Treg* regulatory T cells, *FAs* fatty acids, *SFAs* saturated fatty acids

exerting low side effects and being available at competitive price (Maisuthisakul et al. 2008; Badshah et al. 2021b; Jannat et al. 2021).

Figure 4 describes anti-inflammatory effects of quercetin via regulation of various signaling pathways.

Silymarin has numerous health benefits and exerts its effects via various molecular mechanisms. Figure 5 describes the antiviral, antioxidant, anti-arthritis, anti-inflammatory, antidiabetic, protective and wound healing mechanisms of action of silymarin.

Methods

In this review, the viral agents causing the IBD as well as the antiviral and IBD-protective role of quercetin and silymarin were evaluated according to previous published data. Search engines including Google Scholar, PubMed, Scopus and Web of Science were used. Key words included "inflammatory bowel disease," "viruses," "viral agents," "inflammation," "immunosuppression," "silymarin" and "quercetin." Only related scientific publications were included during 2010–2023. Those publications without full-text availability and non-English papers were excluded. All publications with in vitro, in vivo and clinical trial surveys were included but in silico studies were excluded (Fig. 6).

Viral agents and the IBD

The IBD occurs and develops as a consequence of genetic and environmental factors which further develop the intestinal epithelium inflammation (Molodecky and Kaplan 2010; Sheehan et al. 2015; Kaplan and Windsor 2021). The suppressed or low immune responses following drug consumption play a crucial role in the proliferation of microbial agents leading to viral infections (Masclee et al. 2013; Dudzińska et al. 2018). Among IBD patients, viral infections mostly occur at ages < 35 years and include 40% of total opportunistic infections (Kirchgesner et al. 2018; Wisniewski et al. 2020). Several treatments such as corticosteroids (prednisolone above 20 mg), anti-TNF + thiopurine combination and azathioprine and mercaptopurine (AZA/6MP) have developed viral infections supposedly by suppression of T cells and other immunity responses (Craviotto et al. 2021). Major viral agents causing opportunistic infections in these conditions

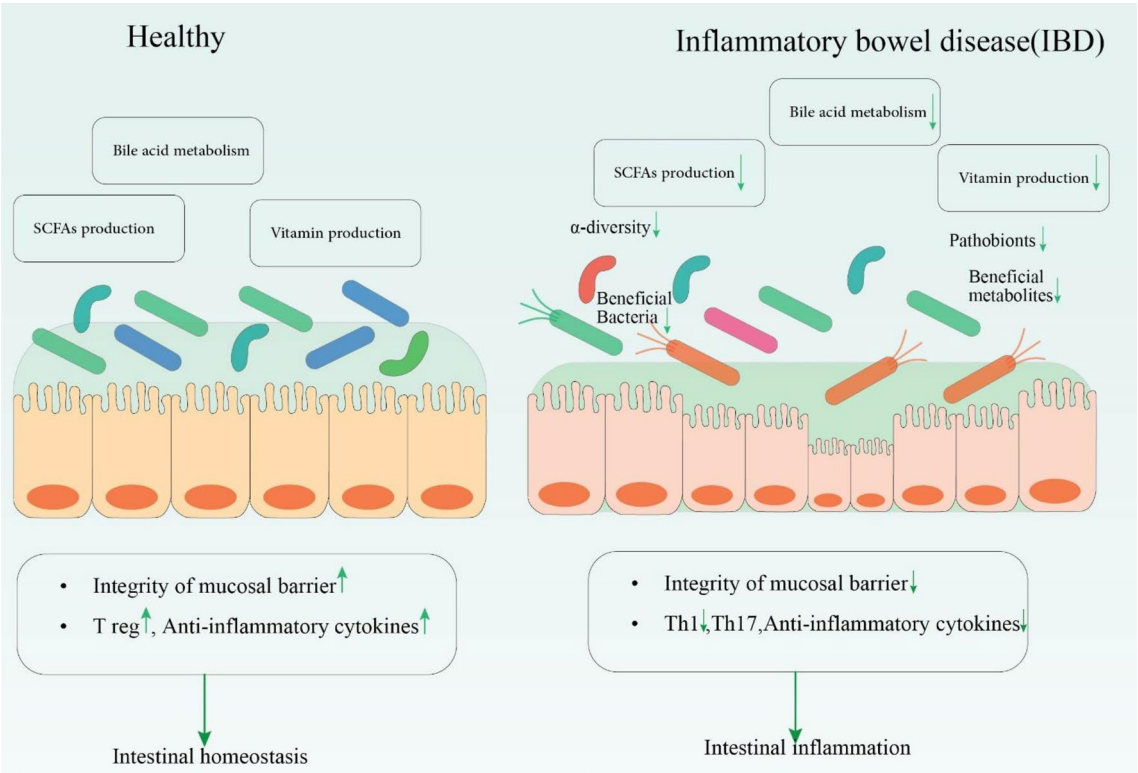
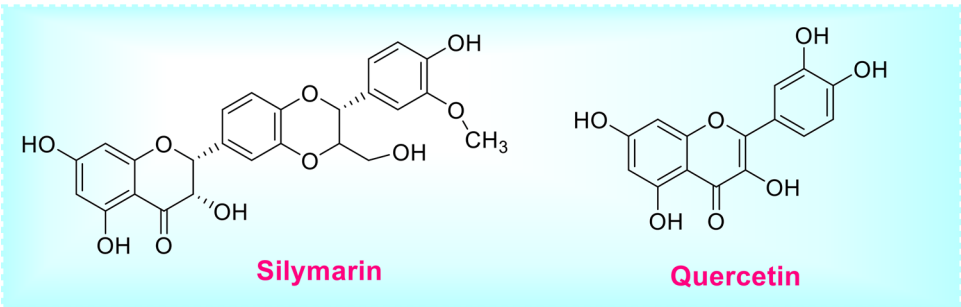


Fig. 2 The imbalance of Gut microbiota causing the IBD progression; a healthy gut preserves intestinal homeostasis via sufficient production of short-chain fatty acids (SCFAs) and vitamins and bile acid metabolism which maintain the balance within the gut microbiota and lessens the inflammation. However, in IBD conditions, these products are decreased leading to a low diversity of beneficial bacteria and their metabolites, resulting in gut inflammation. *Th* T helper cell, *Treg* regulatory T cell

Fig. 3 Structure of quercetin and silymarin



include cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus (EBV) and varicella zoster virus (VZV) (Craviotto et al. 2021). Other viral agents reported in the IBD have included severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), influenza virus types A and B, hepatitis A, B and C viruses (HAV, HBV and HCV, respectively), human papilloma virus (HPV) and human immunodeficiency virus (HIV) (Masclee et al. 2013; Tarris et al. 2021). These infections are consequent to alterations in host responses, including neutropenia and lymphopenia following utilization of immunomodulators. Inadequate immunization of IBD patients is another predisposing factor which leads to excess of hospitalization and increases the burden of costs in the health system. Accordingly, gastroenterologists should be aware of viral infections which are difficult to diagnose posing a high rate of morbidity and mortality. A combination regimen of thiopurines and antitumor necrosis factor α (TNF-α) agents and lower doses of systemic steroids are more effective to restrict opportunistic viral infections. Main mechanisms of IBD development following viral infections include induction of pro-inflammatory cytokines and chemokines, cytokine storm and Th cells multiplication leading to inflammation and epithelium damage (Masclee et al. 2013; Dudzińska et al. 2018; Tarris et al. 2021).

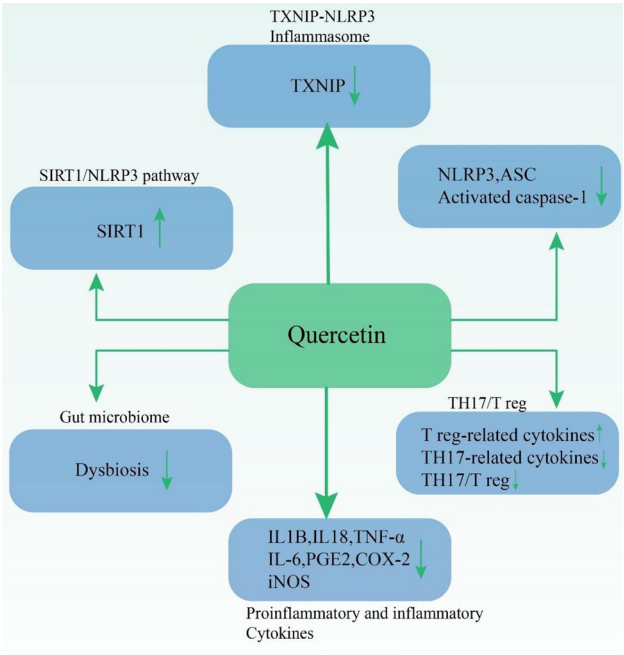


Fig. 4 The anti-inflammatory effects of quercetin via regulation of various signaling pathways such as TXNIP-NLRP3 inflammasome, SIRT1-NLRP3 pathway, NLRP3/ASC caspase activating, gut microbiome maintenance and T cells and cytokines/chemokines regulation; *TXNIP* thioredoxin (TRX)-interacting protein, *NLRP3* NOD-like receptor family pyrin domain-containing 3, *SIRT1* sirtuin (silent mating-type information regulation 2 homolog) 1, *ASC* apoptotic speck-like protein containing a caspase recruitment domain, *Th* T helper cell, *Treg* regulatory T cell, *IL* interleukin, *TNF-α* tumor necrosis factor α, *PGE-2* prostaglandin E2, *COX-2* cyclooxygenase-2, *iNOS* inducible nitric oxide synthase. Silibinin is the major active component of silymarin which also exhibits antioxidative, anticancer and antimicrobial traits (Ravichandran et al. 2010; Mariño et al. 2013; Rendina et al. 2014)

Cytomegalovirus and varicella zoster and IBD

The cytomegalovirus (CMV) is a member of *Herpes viridae* family which has a high rate of infection with lifelong dormant phase around the world in particular among those individuals with compromised immune system (Craviotto et al. 2021). Regarding the CMV pathophysiology, the virus enters monocytes, endothelial cells, fibroblasts or granulocyte stem cells and remains in epithelial cells due to the activity of immune compartments, particularly of natural killer (NK) cells (Jentzer et al. 2020; Mourad et al. 2020). In conditions of impaired NK activity and mucosal immunity or inherent impairment, UC patients are predisposed to the infection. Immunosuppression (impairing T lymphocytes), corticosteroids (causing CMV reactivation), cytokines, especially TNF-α (inducing viral replication) and pro-inflammatory cytokines (IL-6) production (exacerbating the colitis conditions) include mechanisms promoting the CMV-mediated IBD pathophysiology (Lawlor and Moss 2010; Lee and Eun 2022). Conversely, CD4 + T cells produce interferon alpha (IFN-α) in the CD which precludes the CMV reactivation resulting in lower rate of infection and consequent inflammation (Nakase et al. 2010; McCurdy et al. 2015). The CMV and IBD association which can exacerbate the IBD conditions has been described for long years, though debates remains open on the development of severe disease (Powell et al. 1961; Luangsirithanya et al. 2021; O'Connor 2021). The CMV rate of infection in China has been higher in the UC than CD (Yang and Qian 2022). The inflammation of the epithelium is consequent to the stimulation of immune responses by the CMV proteins (Lv et al. 2017). In IBD patients, the proinflammatory cytokines such as TNF-α, interferon-γ and interleukin-2 (IL-2) released by inflammatory or epithelial cells result in the enhancement of chemokines and transcription molecules and subsequent CMV reactivation (Luangsirithanya et al. 2021). The CMV existence in colonic biopsies and its clinical relevance is controversial in spite of observations of refractory illness in pediatric patients (Hommes et al. 2004). However, immunosuppression is associated with the Herpes simplex colitis or UC (Temtem et al. 2021). CMV-associated colitis or UC has been linked to active illness, immunosuppressive medicine, steroid therapy, steroid-refractory disease progression and higher colectomy rates in IBD patients (with high-grade CMV infection) (Kjaer et al. 2018; Mourad et al. 2020; Hazır-Konya et al. 2021; Leal et al. 2022; Ouali and Achkar 2022). CMV has been also associated with early relapse of colitis. Several questions still need to be addressed such as the lack of a global standard definition for this association, the accurate diagnostic test, the exact timing of treatment and the potential role of CMV in the disease (Mourad et al. 2020). Several factors such as advanced age, pancolitis, female gender, low blood leukocytes count, steroids and azathioprine, infliximab (anti-TNF-α) and disease duration less than six months have been associated with the IBD induced by CMV infection (Kishore et al. 2004; Gauss et al. 2015; Campos et al. 2017; Shukla et al. 2017).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a severe respiratory disease (Bezzio et al. 2020; Jena et al. 2022) and novel variants of concern (VOCs) have emerged, conveying different clinical symptoms (Brodin 2021; Kennedy et al. 2021; Yang and Rao 2021). Considering the existence of angiotensin-converting enzyme 2 (ACE-2) receptor onto the respiratory and epithelial cells, the SARS-CoV-2 enters into the enterocytes (Puoti et al. 2021). Therefore, etiopathologic aspects mainly include, impaired ACE-2, absorption loss and GIT inflammation. The cytokine storm induced by SARS-CoV-2 is similar to that of

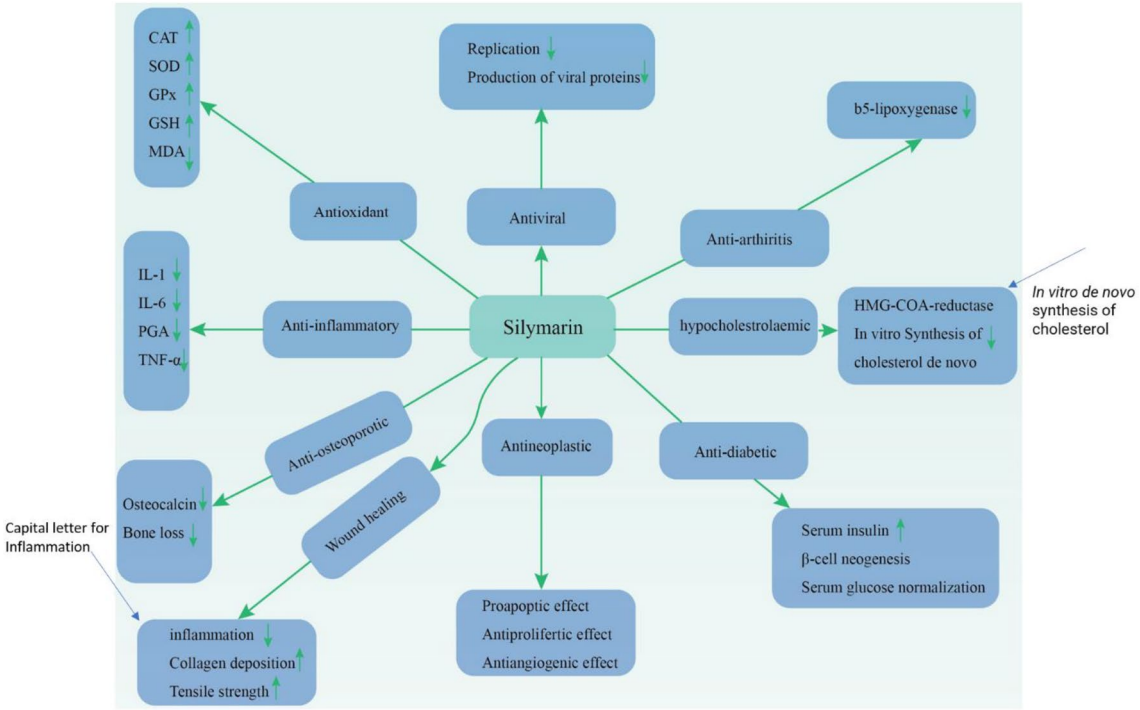


Fig. 5 The protective and effects of silymarin including antiviral, antioxidant, anti-arthritis, anti-inflammatory, antidiabetic protective and wound healing mechanisms; *GPx* glutathione peroxidase, *CAT* catalase, *MDA* malondialdehyde, *GSH* glutathione, *SOD* superoxide dismutase, *PGA* prostaglandin, *IL* interleukin, *TNF-α* tumor necrosis factor α, *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A (Saeed et al. 2017). Details of association of various viral agents in IBD and each flavonoid antiviral effects have not been evaluated. The objective of this review was to provide an update regarding the effects of viral agents on IBD development and antiviral properties of quercetin and silymarin considering their anti-inflammatory effects

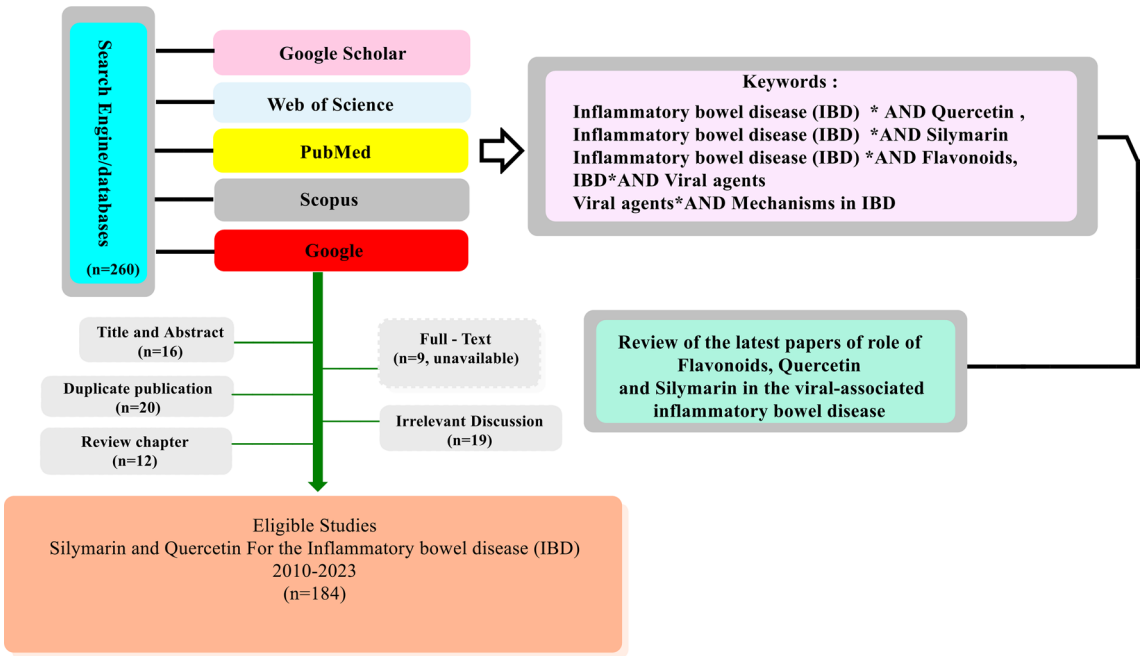


Fig. 6 Flowchart of the methodology applied in this review

the IBD (such as IL-1, IL-6 and TNF-α) (Aziz et al. 2020; Bezzio et al. 2020; Bodini et al. 2020; Barbalho et al. 2021; Hanrahan et al. 2021; Gray-Rodriguez et al. 2022). Notably, consumption of the anti-TNF drug possibly downregulates the anti-SARS-CoV-2 immune responses which increase the pathologic consequences of various agents such as SARS-CoV-2, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) (Abdullah et al. 2020; Neurath 2020; Wisniewski et al. 2020; Lee et al. 2022). A study demonstrated the microbiota dysbiosis following the SARS-CoV-2 infection which leads to IBD progress. They assumed that probiotics supplementation is promising to prevent and heal the IBD (Din et al. 2021). Other studies have not observed such an association regarding the SARS-CoV-2 (Aziz et al. 2020; Bodini et al. 2020; Jena et al. 2022). It is worth mentioning that the expression of trypsin-like proteases being responsible for the spike protein cleavage is increased among IBD patients and facilitate the infection initiation (Neurath 2020; Hanrahan et al. 2021). The ustekinumab drug (anti-p40 mAb) as the IL-12/IL-23 inhibitor has exhibited a therapeutic effect on IBD and SARS-CoV-2 eradication (Monteleone and Ardizzone 2020; Schmidt et al. 2021). As SARS-CoV-2 enhances the inflammation and develops the IBD, flavonoids inhibit various signaling pathways and encounter the cytokine storm following SARS-CoV-2 infection {Liskova et al. 2021). However, their effects on IBD were discussed via effects on NLRP3 inflammasome (Wang et al. 2018).

Epstein–Barr virus

As another member of the herpesvirus family, Epstein–Barr virus (EBV) has infected most of the world's population (90%), in a form of latent lifelong infection, as an asymptomatic disease in childhood and as infectious mononucleosis (IM) in adulthood, a self-limiting disease (Jefremow and Neurath 2020; Zhang et al. 2022). In a systematic review and meta-analysis, using 11 metagenomic studies, the EBV plus CMV was determined as a significant cause of IBD (Marongiu et al. 2022). The EBV infecting B cells has been involved in a variety of autoimmune diseases and cancers (Çolak et al. 2018; Caetano et al. 2021; Wallaschek et al. 2021). Fatal lymphoproliferative disease is caused following viral reactivation mainly among immunosuppressed and vulnerable populations (Vockerodt et al. 2015). The virus has been associated with inflammatory responses, lymphoproliferative disorders (LPD), IBD, CD and UC detected within the epithelial cells (Spieker and Herbst 2000; Ryan et al. 2012; Li et al. 2019b; Wu et al. 2019; Xu et al. 2020; Miura et al. 2021). Long-term use of immunosuppressants or biologics and the inflammation of the epithelium due to the EBV infection result in EBV transformation (mostly within B cells and NK cells) from latent to lytic form, colitis and related lymphoproliferative diseases (Ciccocioppo et al. 2015; Nissen et al. 2015; Münz 2019). The EBV DNA provokes pro-inflammatory responses via toll-like receptor (TLR) signaling (Salloum et al. 2018). The EBV DNA can also enhance the expression of IFN-γ, IL-17A and TNF-α in the in vivo colitis model, exacerbating the colon damage (Wu et al. 2019; Andari et al. 2021) and leading to increase of disease severity (Kato et al. 2021). T cells, B cells and NK cells infections also occur, impairing cellular immunity. Additionally, the spread of infection into enterocytes causes epithelial or mucosal tissue damage (Zhang et al. 2022). The misdiagnosis may occur due to the similarity of IBD and EBV-associated lymphoproliferative disorders (LPDs) (Patton et al. 2018; Zhou et al. 2019).

Enteric viruses and the IBD

Viral enteric pathogens including *Picornaviridae*, *Astroviridae*, rotaviruses, enteroviruses, *Calisiviridae*, sapovirus, adenovirus and norovirus are human and animal pathogens replicating in the GIT (Khetsuriani et al. 2006; Craviotto et al. 2021). Some studies have demonstrated higher number of these enteric viruses in the IBD and CD. These viruses interact with the HBGA-like molecules and increase the inflammatory responses via IFN-β, TNF-α, IFN-γ IL-8, IL-17, IL-10, IL-25, TLR3, Th1 and Th17 enhancement during the IBD, CD and UC (Kolho et al. 2012; Yang et al. 2016). These agents have been increased during immunosuppression such as HIV patients. Rotavirus (RV) particularly species A causes infection of intestinal epithelial cells (IECs) in children. An immunosuppressive drug, 6-thioguanine (6-TG) restricts the RV replication in IBD patients via effect on the Ras-related C3 botulinum toxin substrate 1 (Rac1). The imbalance of gut microbiota such as *Lactobacillus* spp in the ileum has been associated with the increased number of RV. Noroviruses and Adenoviruses bind to α4β1 and α4β7 integrins receptors for leukocytes binding and can increase the expression of sialylated Lewis x (sLex) and Lewis a (sLea) antigens. However, enteric viruses have also reduced the intestinal inflammation via an increase in the IFNβ levels through TLR3 and TLR7 (Ilan et al. 2017; Reddy et al. 2018; Wang et al. 2021).

Hepatitis B and C and the IBD

The existence of HBV among IBD patients has been reported using hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen (HBsAg/anti-HBs). A higher rate of HBsAg has been reported in previous studies (Ilan et al. 2017; Reddy et al. 2018). Due to the lack of sufficient vaccination against HBV among developing countries and higher levels of viral infection, the associated IBD risk has increased (Loras et al. 2010; Childs et al. 2018). The

virus status and type of treatment determine the recurrence of HBV. The antiviral therapy should be continued for up to 6 months after immunosuppressive drugs intake (Park et al. 2020). The immunosuppressive treatment (anti-integrin drugs, infliximab, anti-TNF) of IBD patients is a risk factor for the recurrence of infection and poor response to HBV vaccination, resulting in hepatic fibrosis (through WNT-signaling PI3K/Akt/mTOR Ras/ERK1/2 and p53 pathways), impairment and death (Dougan et al. 2021). Therefore, sufficient immunity stimulation through vaccination prior to the treatment is pivotal for infection control. Notably, the anti-HBV response is mitigated among IBD patients even during vaccination.

The rate of HCV is estimated to be 0.7–2.5% worldwide (Lin et al. 2013; Blach et al. 2022). Drug injection, dialysis, Hansen's disease or hemophilia, and maternal transmission are risk factors. HCV-positive IBD patients have developed auto-antibody responses which destroy the liver. It was found that INF therapy has no significant effect on the progress of IBD in HCV-positive patients. Pyoderma gangrenosum (PG) is also associated with HCV (Croitoru et al. 2021). Interestingly, age does not seem to be a determinant factor in the infection since a recent study in Italy revealed that older age is not affecting viral hepatitis–IBD association (Losurdo et al. 2020). Patients infected with genotype-1 and genotype-3 HCV have been more predisposed to develop colitis with higher ghrelin concentrations (Pavlidis et al. 2011). The decreased rate of publications regarding the HCV and the IBD association reflects the decreased HCV risk due to higher adherence to preventative measures and better aseptic perioperative rules (Flores et al. 2022; Giri et al. 2022).

Other viral agents in the IBD

The mechanism of influenza virus types A and B involved in the IBD progression has not been fully understood. Apparently, the virus effects on the GIT are mediated by the inhibition of gut microbiota-associated immune responses. In addition to the respiratory infection, mainly due to lower immune responses in IBD patients, other clinical signs are associated with the influenza virus. Furthermore, respiratory infection causes the migration of Th17 cells into the intestine and the first secretion of INF-γ followed by IL-15 which affects the microbiome (Zullow and Farraye 2019). TNFα and CD8 + T cells increase too. A study on 140,480 patients outlined a significant higher rate of influenza virus in IBD patients compared to the controls (Tinsley et al. 2019; Caldera et al. 2020). The effect of the influenza vaccination among IBD patients is also controversial advocating the use of repetitive doses of influenza vaccine or new strategies (Froggatt and Heaton 2022). In a study in Germany, on 99 IBD patients, 11 percent were positive for human papilloma virus (HPV) (Brunner et al. 2022). Treatment with thiopurines in IBD patients increases the viral infection and skin warts. Among 58,979 IBD patients, 145 of them were infected with HIV. Patients with UC and HIV had higher hospitalization rates, with consequent minor charges and costs compared to those HIV-negative patients (Then et al. 2021). It was stated that management of comorbid IBD and HIV in patients is possible using immunosuppressive drugs. However, their effect on $CD4^+$ levels should be assessed (Hunt et al. 2021). It was also concluded that HIV persistence in UC could be challenged through a strong gut barrier integrity and reduction of inflammation (Peng et al. 2021).

Quercetin protective effects on the viral-associated IBD

Quercetin (Fig. 5) is a polyphenol, naturally found in different fruits, vegetables, seeds, red onions, berries, teas and kale (Ju et al. 2018). The IBD protective role of quercetin is due to PI3K inhibition and decrease of proinflammatory cytokines and chemokines, MMP-9, TNF-α, iNOS, ICAM-1 and CD4 + T cells (Nair et al. 2002; Comalada et al. 2005; Yu et al. 2008; Huang et al. 2010; Di Petrillo et al. 2022). Quercetin also contributes to inhibiting mast cells degranulation, Th2 cells, neutrophils, eosinophils and macrophages proliferation. Various mechanisms of action have been mentioned such as maintenance or increasing the gut microbiota diversity, nitric oxide (NO) or iNOS reduction via NF-κB downregulation, mitogen-activated protein kinase (MAPK) pathway (via toll-like receptor 4) and suppression of proinflammatory mediators or inflammatory proteins production via antioxidant effects. Additionally, anti-apoptotic effects, heme oxygenase-1 (Hmox1, HO-1) in colitis, downregulation of MMP-9, TNF-α and ICAM-1, increase in anti-viral type I interferon, inhibition of cytokine storm, senescence and cell cycle arrest have been also demonstrated (Yang et al. 2018; Cheng et al. 2019; Li et al. 2019a).

Quercetin enhances the colonic glutathione (GSH) reservoirs and nuclear factor erythroid 2-related factor 2 (Nrf2), protecting the intestinal porcine epithelial cell line 1 (IPEC-1) cells (Jia et al. 2021). It was also stated that quercetin activates anti-viral macrophages (dsRNA-induced) via the calcium-STAT pathway in vivo. Quercetin is metabolized by the gut microbiota into various beneficial compounds such as SCFA (short-chain fatty acids), homoprocatechuic acid, bacteriocins, amino acids, propionic acid, vitamins and bile acids. Moreover, quercetin has inferred anti-viral effects against hepatitis B and C, SARS-CoV-2, dengue virus (DENV), H1N1, H3N2, poliovirus, rhinovirus, chikungunya virus (CHIKV), MERS-CoV, herpes virus and Epstein–Barr virus (Cheng et al. 2015; Rojas et al. 2016; Frederico et al. 2017; Zakaryan et al. 2017; Colunga Biancatelli et al. 2020) (Table 1). An in vitro study exhibited that

Table 1 The antiviral effects of quercetin

Concentration	Virus	Mechanism or effect	References
1.1 µg/mL	DENV	NS5 protein binding	Dewi et al. (2019)
0.2 µg/mL	Rhinovirus	Inhibition of replication	Ganesan et al. (2012)
Network pharmacology	Epstein–Barr virus, hepatitis C, measles, herpesvirus,	Bcl-2, PTGS2 and caspase 3 effect, ACE2 binding, replication and assembly	Jimilihan et al. (2020)
2 µg/mL	Poliovirus	RNA synthesis inhibition	Castrillo et al. (1986)
1 mM	CHIKV	HSP 70 inhibition	Ghosh et al. (2017)
Molecular docking, Network and traditional	SARS-CoV-2	Caspase 3, MAPK, interleukins, CLR signaling pathway, spike, replication, PI3K/Akt signaling pathway, JAK-STAT, TLRs, cyclooxygenase 2, g PI3K-Akt signaling pathway,	Huang et al. (2020), Sun et al. (2020), Vijayakumar et al. (2020), Wang et al. (2020)
2 µg/mL	Poliovirus	Blocking RNA synthesis	Castrillo et al. (1986)
7 µM	MERS-CoV	3Clpro protease inhibition	Jo et al. (2019)

NS5 non-structural protein 5, *PTGS2* prostaglandin-endoperoxide synthase 2, *ACE2* angiotensin converting enzyme 2, *HSP* heat shock protein, *MAPK* mitogen-activated protein kinase, *CLR* c-type lectin receptor, *CHIKV* chikungunya virus, *SGIV* Singapore grouper iridovirus, *PI3K/Akt or PKB* phosphatidylinositol 3-kinase/protein kinase B, *MERS-CoV* Middle East respiratory syndrome coronavirus

quercetin exerted virucidal effects against equid herpesvirus 1 (EHV-1) at 0 and 1 h of replication (Gravina et al. 2011). Considering low levels of diet quercetin absorption in the GIT or IBD, effective formulations are needed to increase its bioavailability (Salaritabar et al. 2017). Another derivative of quercetin, rutin, a flavonoid quite abundant in the human diet (fruits and vegetables), exerts antimicrobial and antioxidant effects. Glycosylated forms of quercetin and rutin exhibit enhanced intestinal absorption in animal models (Patel and Patel 2019; Zhou et al. 2021). The quercetin plus quercitrin but not rutin exhibited synergistic activity against the DENV (Chiow et al. 2016).

Quercetin has given satisfactory clinical outcomes for individuals with IBD, colitis and CD conferring anti-inflammatory and antioxidant effects. However, the compound has poor oral bioavailability and absorption (Diniz et al. 2020). Quercetin safety dose is 1000 mg/m^2 (Hollman et al. 1997). Anti-SARS CoV-2 effects of quercetin included reduced hospitalization incidence and intensive care unit residence (Cheema et al. 2023). Quercetin restores immune homeostasis and colonic microbiota and consolidates the intestinal barrier (Lyu et al. 2022). The metabolic regulatory and senolytic activity of quercetin have been described. Satisfactory outcomes have been reported following the consumption of quercetin and drugs in kidney disease, metabolic syndrome following obesity and pulmonary fibrosis (Guo et al. 2019; Hickson et al. 2019; Dziąbowska-Grabias et al. 2021; Hosseini et al. 2021; Gonzales et al. 2022). The clinical outcomes of the quercetin on the IBD remain to be fully understood needing further investigations (Lyu et al. 2022).

Silymarin protective effects on the viral-associated IBD

Silymarin bioactive compound is obtained from *Silybum marianum* seeds with high anti-inflammatory activity. Silibinin or silybin is the major and active compound of silymarin that is a mixture of two diastereomers, containing silibinin A and silibinin B, in approximately equimolar ratio (Nikonov et al. 2017). Silymarin has been shown to possess strong antiviral activities against various viral agents by targeting several steps of the viral replication cycle. Its hepatoprotective effects are well documented. Some researchers have confirmed that silymarin has a special effect on the control of immune-based murine colitis by healing the bowel histology in vitro and promoting the decrease of bowel inflammatory cytokines, especially TNF-α, interleukin-1β (IL-1β) and nuclear factor κB (NF-κB) (Davis-Searles et al. 2005; Zou et al. 2021). The in vitro, in vivo and in silico studies of silymarin as attractive antiviral candidates against different viruses are described in Table 2.

Recently, clinical trial studies (Table 3) on silymarin and its derivatives have been focusing on HCV infections and particularly the antiviral activity of silymarin against chronic HCV.

Silymarin has demonstrated antioxidant and anti-inflammatory properties, protecting hepatic cells from damage. Clinical outcomes of silymarin have been delineated in UC in which 35/38 of patients recovered satisfactorily compared to the control group after 6 months (Rastegarpanah et al.

Table 2 The antiviral effects of silymarin

Concentration	Virus	Mechanism or effect	References
10 and 20 µg/mL	Hepatitis C	Potentiation of the JAK-STAT antiviral signaling pathway	Polyak et al. (2007)
75−100 µM	Hepatitis C	Inhibition of NS5B polymerase activity and blocking viral entry and transmission	Wagoner et al. (2010)
75−100 µM	Hepatitis C	Inhibition of the NS5B RNA-dependent RNA polymerase	Ahmed–Belkacem et al. (2010)
50 or 80 µM	Hepatitis C	Silibinin impeded HCV endosomal tracking and blocked CME	Blaising et al. (2013)
67.6 mM	Hepatitis C	Inhibition of HCV NS4B and hence the membranous web morphogenesis	Esser-Nobis et al. (2013)
Nanoscale spherical particles (< 200 nm) encapsulating amorphous silibinin at > 97% efficiency	Hepatitis C	Inhibition of HCV cell-to-cell spread and attenuation of HCV infection of PHHs	Liu et al. (2017)
469, 265 or 61.5 mg/kg chimeric mice	Hepatitis C (in vivo) Intravenous	Blocked HCV production and increased anti-inflammatory and anti-proliferative gene expressions without affecting serum albumin levels	DebRoy et al. (2016)
6.25–100 µM	Influenza A virus (IAV)	S0 and S3 inhibited IAV replication and disrupted the formation of the Atg5-Atg12/Atg16L complex	Dai et al. (2013)
100 µg/ml	Influenza A virus (IAV)	Inhibition of late viral RNA synthesis	Song and Choi (2011)
25 mg/kg/day Oral	AV infection of BALB/c mice (in vivo)	S0 and S3 increased the survival rate of mice (40% and 60% respectively) and S3 decreased virus titers in the lungs (100-fold)	
Docking to NS4B	DENV	All three silymarin derivatives docked with high binding affinity (≥ − 8 kal/mol) to DENV NS4B	Qaddir et al. (2017)
100 µg/ml	CHIKV	Inhibition of CHIKV replication and protein synthesis	Lani et al. (2015)
2 µg/ml	Human immunodeficiency virus (HIV)	Attenuating cellular functions involved in T cell activation, proliferation and HIV infection	McClure et al. (2012)
125 µM	Human immunodeficiency virus (HIV)	Perturbation of T cell metabolism in vitro; Legalon® SIL additionally blocked HIV infection of T cells	McClure et al. (2014)
0–200 µM	Hepatitis B virus (HBV)	Blockade of clathrin-mediated endocytosis	Umetsu et al. (2018)
30, 100 and 300 mg/kg/d (Oral)	HBV X protein (HBx) transgenic mice (in vivo)	Silymarin had no effect on HBx expression and late stage carcinogenesis, but recovered fatty acid change and liver pathology in the early stages of liver damage	Wu et al. (2008)
6.25–25 µg/ml	Mayaro virus (MAYV)	Inhibition of replication and ROS induction	Camini et al. (2018)

JAK-STAT Janus kinase-signal transducer and activator of transcription, *NS5B* nonstructural protein 5B, *DENV* dengue virus, *CHIKV* chikungunya virus, *HCV* hepatitis C virus, *PHHs* primary human hepatocytes, *ROS* reactive oxygen species

2015). Clinical improvement of UC and CD has been demonstrated in some studies (Hagan et al. 2021). Another study revealed the antiviral effects of silymarin against COVID-19 (Palit et al. 2021).

Table 3 Clinical trials of silymarin antiviral effects against HCV

Virus	Concentration	Country	Year	Age	Number	References
HCV	140–700 mg, 3 times per day (for 24 weeks) 12 months	Egypt	2004	Children less than 18 years of age	141 infected patients	Tanamly et al. (2004)
HCV	250 mg once daily or twice a week for the first 10 week for 24 week	Israel	2007	Age of 18–75 year	100 chronic infected patients	Gabbay et al. (2007)
HCV	420 mg silymarin, 700 mg silymarin, or matching placebo administered 3 times per day for 24 weeks	United States	2011	Median age was 54 years,	154 chronic HCV infected patients	Fried et al. (2012)
HCV	Silybinvitamin E-phospholipids in patients with chronic hepatitis C, 1.5 mg/kg per week, Silybin 47 mg + vitamin E 15 mg + phospholipids 97 mg in two pill for 12 months. after 6, 12 months and at follow up	United States	2015	45 year	32 chronic infected patients	Malaguarnera et al. (2015)
HCV	1.5 mg/kg per week of Peg–IFN plus RBV and placebo, while Group B received the same dosage of Peg–IFN plus RBV plus association of Silybin 94 mg + vitamin E 30 mg + phospholipids 194 mg in pills for 12 months	Italy	2013		62 patients	Malaguarnera et al. (2016)
HCV	10 mg/kg/day Silibinin IV 16 patients received 10 mg/kg/day SIL IV (Legalon Sil; Madaus, Köln, Germany) for 7 days. In a subsequent dose-finding study, 20 patients received 5, 10, 15, or 20 mg/kg/day SIL for 14 days	Germany	2008		20 patients	Ferenci et al. (2008)
HCV	25 patients receiving 10, 15, or 20 mg/kg/day of SIL	USA	2012		25 patients	Guedj et al. (2012)
HCV	7-day course of 5, 10, 15, or 20 mg/kg per day of silibinin	Germany	2009	65-year-old	Six patients	Biermer and Berg (2009)
HCV	Silibinin 20 mg/kg/day intravenously for 14 or 21 days	Italy	2011		27 treatment-naive patients	Rutter et al. (2011)
HCV	Sofosbuvir and Ribavirin 400 and 800 mg per day along with silymarin (400 mg per day)	Pakistan	2022	8–50 years of age	30 patients	Ahmed et al. (2022)

HCV hepatitis C virus, *INF* interferon, *RBV* ribavirin, *SIL* silibinin, *IV* intravenous

Future prospects

Considering the pivotal role of inflammation in IBD development, the study and application of anti-inflammatory quercetin and silymarin bioactive compounds is greatly encouraged. The combination of these bioactive compounds with antivirals is also a proper strategy for antiviral therapy (Ninfali et al. 2020). However, due to low GIT bioavailability, stability and absorption concerns, their chemical modification and formulation and application of drug delivery systems need further investigation. On the other, immune suppression by chemotherapeutic drugs leads to the reactivation of infections such as existing or latent viral agents. Therefore, application of safe natural bioactive compounds with anti-inflammatory and antiviral effects is promising. Protein targeting and destroying the major viral agents causing epithelial cells inflammation (IBD development) are also promising, as well as future ligand-receptor interaction assessing studies. Natural databases are also available to be screened for the selection of potential bioactive compounds with anti-inflammatory and antiviral properties prior to the implementation of experimental studies. Another aspect of bioactive compounds utilization in IBD treatment is their stability in the GIT which deserves further in-depth investigation (Chang et al. 2022). Proper drug delivery systems can be applied for a more efficient treatment by targeting the right dose of compounds to the precise destination sites (Chai et al. 2018; Gonçalves et al. 2021).

Conclusion

The immunosuppression during the IBD treatment is associated with the proliferation of various viral agents such as CMV, EBV, HIV, HPV, HBV, HAV, HCV and influenza virus. Various genetic, epigenetic or environmental factors also contribute to exacerbate IBD severity. The exact mechanisms of enteric viruses' pathophysiology in the IBD development remain to be clarified. Herein, we determined potential viral agents increasing the risk of IBD and unveiled their mechanisms using published data. HMs-derived flavonoids are promising in this context to preclude inflammation and virucidal effects. Quercetin and silymarin have shown IBD protective effects such as antiviral traits and immunomodulation. Mechanisms of protection and antiviral effects of these bioactive compounds include decrease of oxidative damage, inhibition of viral binding and replication, RNA synthesis, caspase enzymes, viral proteases and viral assembly. The consumption of quercetin and silymarin is promising for viral-associated IBD prevention and treatment. Other natural bioactive compounds could be also considered as potential natural remedies to fight against IBD. Further studies are warranted regarding the formulation of these bioactive compounds in antimicrobial and anti-inflammatory treatment for IBD.

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