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REVIEW

A review of the biological and pharmacological activities of *mesalazine* or *5-aminosalicylic acid (5-ASA)*: an anti-ulcer and anti-oxidant drug

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Abstract

Mesalazine, also known as 5-aminosalicylic acid (5-ASA), is a synthetic drug from the family of nonsteroidal anti-inflammatory drugs (NSAIDs) used for inflammatory diseases of the gastrointestinal tract. However, 5-ASA has also been used for various other diseases due to its pharmacological effects, but they are usually scattered across various publications, which may limit further research and clinical use of this drug. This review is a summary of published information on the biological and pharmacological effects of 5-ASA with the aim of identifying its anti-oxidant role and medicinal use. 5-ASA data have been collected from 1987 to February 2021 using major databases such as Web of Science, PubMed, Elsevier, Wiley Online Library, Springer, Google Scholar, etc. According to research, the pharmacological and biological effects of 5-ASA include treatment of inflammatory bowel disease, and anti-oxidant, anti-inflammatory, antibacterial, antifungal, anticancer, anti-amyloid, gastric protection (gastroprotective), and antidiverticulosis properties. Numerous pharmacological studies have shown that 5-ASA is an anti-oxidant and anti-ulcer compound with high therapeutic potential that, if the appropriate dose is discovered, its chemical structure changes and its effectiveness is optimized, 5-ASA has been used experimentally for other diseases.

Keywords Mesalazine · 5-ASA · Pharmacological effects · Anti-amyloid · Gastroprotective

Introduction

Mesalazine (Fig. 1), also known as mesalamine and 5-aminosalicylic acid (5-ASA), has been used for over 40 years to treat inflammatory bowel disease (IBD) (ulcerative colitis (UC), and mild to moderate Crohn's disease). 5-ASA is a major component of the sulfasalazine (SSZ) drug, which is separated in the large intestine by bacteria containing the enzyme azoreductases by breaking the azo bond from sulfapyridine (SP); SP is one of the components of SSZ, which transports 5-ASA to the colon. Also, this synthetic compound, which belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs), is an anti-oxidant with high biological activity among NSAIDs. Its molecular formula is $C_7H_7NO_3$ and its molecular weight is 153.14 g/mol^{-1}. The IUPAC name of this drug is 5-amino-2-hydroxybenzoic acid, and its brand names are listed in Table 1 (Ci 2014; Scholar 2009).

Despite several methods of synthesis of 5-ASA, so far no new structural changes to increase the pharmacological activity of this synthetic anti-oxidant have occurred. Also, some new commercial brands of 5-ASA, although produced to prevent the consequences of SSZ, have not been completely effective and are not all free from side effects. Usually, side effects include joint pain, muscle pain, bloating, abdominal pain, nausea, diarrhea, headache, etc. (Sehgal et al. 2018; Sardo et al. 2019). On the other hand, in recent years, much in vivo and in vitro research has been carried out on the pharmacological and biological effects of 5-ASA in diseases other than UC and Crohn's disease. These new studies have been mainly on the methods of its delivery to the colon (Canevari et al. 2009), as well as examining its antimicrobial effects (Lin and Pimentel 2001), the prevention of liver fibrosis (Ramadan et al. 2018), inhibition of amyloid fibrils formation (Faramarzian et al. 2020), renal ischemia–reperfusion injury (Pazoki et al. 2005), scavenging of reactive oxygen and nitrogen metabolites, and interference with cellular signaling pathways (e.g., those of NF-κB,

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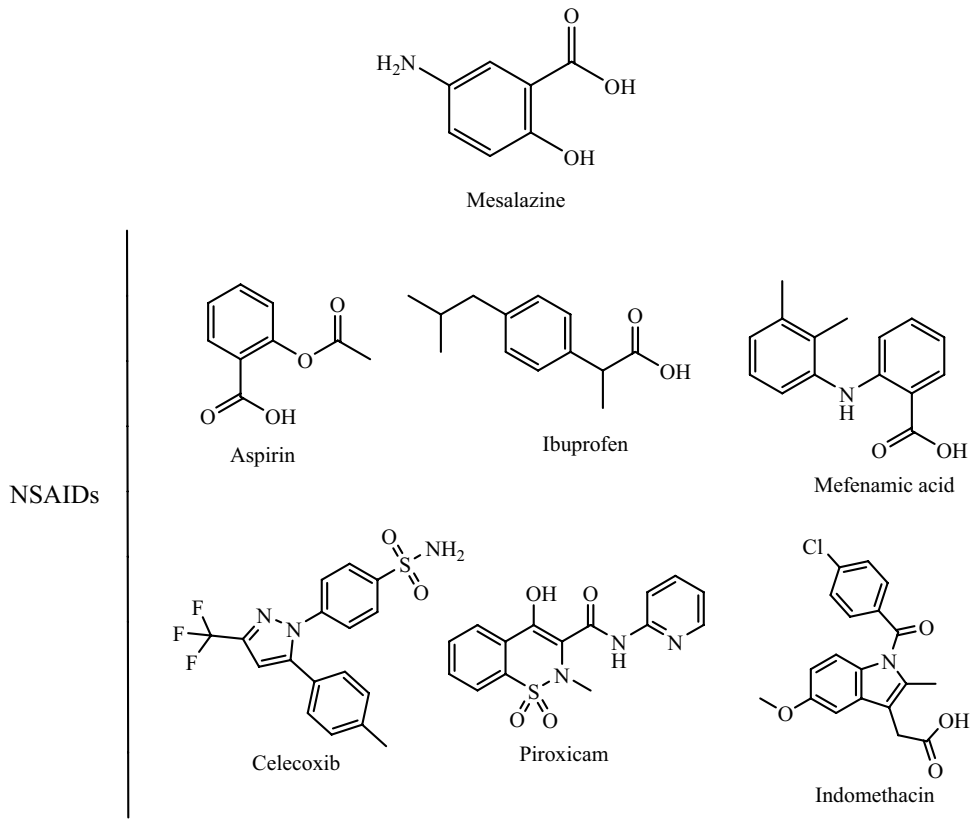

Fig. 1 Chemical structures of common non-steroidal anti-inflammatory drugs (NSAIDs) and 5-ASA

Table 1 The most common brand names of 5-ASA

Mesalazine	Asacol	Claversal	Fisalamine
Pentasa	Mesasal	Rowasa	Salofalk
Lixacol	Lialda	Apriso	Mezavant
Canasa	Lazalan	Quintasa	Salisofar
Asacolitin	Dipentum	Colazide	Ipocol

PPAR-γ, or Wnt/b-catenin) (Yang and McCormack 2011). Also, some researchers have shown that 5-ASA is effective in the prevention and treatment of colorectal cancer (Stolfi et al. 2012), gastric ulcers (Beiranvand and Bahramikia 2020), peritonitis (inflammation of the peritoneum) (Sener et al. 2018), asthma (Raju et al. 2014), wound healing (Sanapalli et al. 2018), chronic beryllium disease (Day et al. 2018), cardiac fibrosis (Hoffmann et al. 2020), and diverticular disease (Comparato et al. 2007).

Considering that the side effects, toxicity, and pharmacokinetics of 5-ASA have been discussed in detail in previous review articles, the purpose of this article is to review and summarize the latest developments in the field of drug effects and biological activities of this drug. I hope that this study can help discover the greater medicinal value of this famous synthetic anti-oxidant, and find ways to increase its pharmacological and biological activity.

Materials and methods

This review paper collected the literature published prior to February 2021 on the pharmacology and biological activities of 5-ASA. All relevant information on 5-ASA was gathered from worldwide accepted scientific search engines and databases, including Web of Science, PubMed, Elsevier, ResearchGate, Wiley Online Library, Springer, Google Scholar, and Scientific Information Database. Most of the cited information in this article was from peer-reviewed journals published in English. Information was also obtained from MSc dissertations and from chapters of specialized books. No time period limitation was considered in this investigation. Moreover, I did not limit 5-ASA studies to clinical cases. Both in vivo and in vitro studies have been systematically included in this review.

Biological activities and pharmacology

Antioxidant and anti-Inflammatory activity

UC is a relapsing inflammatory bowel disease whose pathogenesis has yet to be completely defined. Among UC pathological findings, inflammatory mediator profiles

can change and be associated with inflammation. Various cytokines, especially classical cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 and identified inflammatory mediators play an important role in UC. The cells related to UC pathogenesis consist of antigen-presenting cells (APCs) and T cells. The initiation of UC pathogenesis originates from unknown antigen presentation of intestinal APCs. APCs play a critical function in the initiation of UC immunopathogenesis by releasing cytokines that actively regulate inflammation.

Dendritic cells (DCs) are APCs that play a role as sentinels. They are specialized cells of the immune system that act in systemic and mucosal tissues by endocytosing antigens. DCs have pattern-recognition receptors such as innate immune receptors, including Toll-like receptors (TLRs) that respond to common macromolecules and NOD-like receptors that respond to intracellular and/or extracellular pathogens. Activated DCs secrete pro-inflammatory cytokines and chemokines to intercede the inflammatory regulation in UC through activation of TLRs, which induce infiltration of polymorphic neutrophils and the activation of other innate immune cells.

Macrophages are located in the mucosa of the entire gastrointestinal tract, are found in abundance in the lamina propria, and activate adaptive responses locally in tissue where the antigen is present. They are activated by pathogen-associated molecular patterns via TLRs and secrete proinflammatory cytokines, TNF-α, IL-1, and IL-6. In addition, macrophages secrete reactive species of oxygen and nitrogen as well as proteases that destroy the extracellular matrix. The phenotype of macrophages is shifted to M1 in UC patients, presenting high secretion of pro-inflammatory cytokines and enhancing cytotoxicity and phagocytosis. Therefore, when repairing the intestinal mucosa, reducing the penetration of macrophages and neutralizing the resulting reactive metabolites play an essential role during the progression of inflammation and disease recovery (Tatiya-Aphiradee et al. 2019).

5-ASA as an iron chelator, scavenger of free radicals, and anti-oxidant plays a role in various diseases, including IBD (Allgayer et al. 1992; Ahnfelt-Rønne and Nielsen 1987). At IBD leukocytes produce superoxide anion and hydrogen peroxide and secreted myeloperoxidase (MPO) into the extracellular medium. MPO catalyzes the oxidation of Cl^- by H_2O_2 to yield chlorinated oxidants (e.g., HOCl and NH_2Cl), which have been shown to induce pathologic changes in mucosal function. On the other hand, in a laboratory study, 5-ASA was shown to inhibit the oxidation of L-cysteine by NH_2Cl, HOCl and H_2O_2. In this study, it has been found that pretreatment and incubation of L-cysteine with 5-ASA inhibits the oxidation of L-cysteine by these neutrophil-derived oxidant mediators (Tamai et al. 1991). Also, evidence suggests that lipid peroxidation may play an important role in the pathogenesis of diseases. Therefore, hemoglobin (Hb)-catalyzed peroxidation phospholipid of H_2O_2-dependence as a model of oxidative injury to membrane lipids has been used to assess the ability of 5-ASA. It has been found that, in this model, Hb interacted with H_2O_2 to yield the radical and non-radical forms of ferryl Hb (Hb^{IV}) which were capable of initiating the peroxidation of a phospholipid. In this study, the concentration of 5-ASA required to inhibit lipid peroxidation by 50% (IC_{50}) has been determined to be 50 μM. The mechanism by which 5-ASA inhibited lipid peroxidation appeared to be due to its ability to donate electrons and thus scavenge the radical and non-radical forms of Hb^{IV}. As a result, taken together, the data suggest that 5-ASA is very effective in inhibiting lipid peroxidation catalyzed by hemoproteins such as Hb (Yamada et al. 1991).

In an investigation on the free radical scavenging reactions of SSZ, 5-ASA, and SP using a nanosecond pulse radiolysis technique coupled with transient spectrophotometry to generate free radicals in situ and follow their reaction paths, it was shown that SSZ, 5-ASA, and SP efficiently scavenged e^-_{aq}, $^\bullet CO^-_2$, $^\bullet OH$, $N^\bullet_3$ and $^\bullet CCl_3O_2$ radicals. Also, 5-ASA scavenged glutathiyl, tryptophanyl, and lipid peroxyl radicals, and SSZ scavenged lipid peroxyl and superoxide radical. It is evident from this study that 5-ASA is the most effective moiety involved in the anti-oxidant action of SSZ and its metabolites. In the anti-oxidant activity of SSZ, the phenoxyl group of 5-ASA acts as an electron (or H-atom) donor. One electron-oxidized SSZ, SP, and 5-ASA are scavenged by ascorbate. This study suggests that the free radical scavenging activity of 5-ASA may be the major mode of action of SSZ in IBDs (Joshi et al. 2005).

5-ASA has therapeutic efficacy in IBD, which may be based on its anti-oxidant properties. In one study, perinaric acid was used as a marker of fluorescent oxidation in an intestinal microvillous brush border membrane preparation. Then, various concentrations of the anti-oxidants 5-ASA, ascorbate, and tocopherol were added. Following that, oxidation was initiated from within the membrane by 2,2′-azobis (2,4-dimethylvaleronitrile) (AMVN) and from solution by 2,2′ azobis (2-amidinopropane) hydrochloride (AAPH). The result of this study was that 5-ASA was able to inhibit oxidation initiated from either source, and then from tocopherol against AAPH, and was also more effective against AMVN. It is thought that water soluble 5-ASA preferentially associates with the membrane surface, allowing chain-breaking anti-oxidant activity when peroxidation is initiated within the membrane. Likewise, it is effective against aqueous oxidants because its position allows it to interact with AAPH before lipid peroxidation can be initiated, as well as breaking the lipid peroxidation chain once it is initiated. This dual capacity may be important for the

therapeutic effect of 5-ASA, and suggests it as a candidate anti-oxidant for clinical trials (Pearson et al. 1996). Also, 5-ASA, the therapeutically active metabolite of SSZ, has been exposed to oxygen-derived free radicals produced by the Fenton reaction in vitro. Several metabolites were detected and characterized by high-performance liquid chromatography and ultraviolet spectrophotometry. The majority of these metabolites were present in methanolic extracts of feces samples from SSZ-treated patients with IBD. The presence of these metabolites, which have not been demonstrated in vivo before, provides evidence of an interaction between 5-ASA and oxygen-derived free radicals in SSZ-treated patients with IBD. The concentration of lipid peroxides (which depend on the release of oxygen-induced free radicals) was significantly increased in pre-treatment rectal biopsies of 15 patients. However, after 5 weeks of treatment, the amount of malondialdehyde (MDA) as a marker of lipid peroxide was normalized along with a significant improvement in disease activity. This indicates the important role of the radical scavenging mechanism by 5-ASA in SSZ for the treatment of chronic IBD (Ahnfelt-Rønne et al. 1990). Moreover, studies have shown that 5-ASA decreases reactive oxygen species (ROS) in colonic progenitor cells and increases the expression of the anti-oxidant catalase. Also, in patients with ulcerative colitis treated with 5-ASA, phosphatase and tensin homolog activity was enhanced, thus attenuating PI3K/Akt signaling. The assessment of these studies is that the anti-oxidant properties of 5-ASA may be the dominant mechanism for its chemoprevention (Managlia et al. 2013).

It has recently been reported that 5-ASA reduces indomethacin-induced toxicity by inhibiting intracellular ROS and indomethacin-induced apoptosis, as well as by increasing superoxide dismutase 2 (SOD2) activity, and improves indomethacin-induced wounds in IEC-6 cells (a line of small intestinal cells). This has been attributed to the role of 5-ASA as a free radical scavenger and its anti-oxidant function in the intestinal mucosa (Jung et al. 2020). The exact mechanism of action of SSZ or its metabolites (5-ASA and SP) is not fully understood; however, its anti-oxidant effects are well established and its mechanism of action is probably due to its scavenger effects against ROS and reactive nitrogen species (RNS), as well as its metal-chelating properties, in association with its inhibitory effects over neutrophil oxidative bursts. For this reason, one of the previous studies focused on the screening and comparing inhibitory activity for a set of ROS ($O_2^{\bullet -}$, H_2O_2, $^1O_2$, $ROO^{\bullet}$ and HOCl) and RNS ($NO^{\bullet}$ and $^{-}ONOO$) mediated by SSZ and its metabolites, 5-ASA and SP, using validated in vitro screening systems. The study found that 5-ASA and SSZ were able to scavenge all the tested ROSs, while SP was virtually ineffective in all the assays. 5-ASA for $^1O_2$, $ROO^{\bullet}$ and HOCl has shown the best scavenging effects. A new and important finding from this study was the strong scavenging effect of 5-ASA against $^1O_2$. 5-ASA has also been shown to be a potent scavenger for $NO^{\bullet}$ and $^{-}ONOO$. SSZ was also able to scavenge this RNS, albeit at a much lower potency than 5-ASA (Couto et al. 2010).

Growing experimental data suggest that an inflamed bowel or large intestine may be exposed to significant oxidative stress. The most likely source of these oxidants is phagocytic leukocytes, because these cells are abundant in inflamed mucosa and are known to produce significant amounts of potentially harmful ROS in response to inflammatory stimuli (Yamada et al. 1990). These ROS can initiate and/or amplify inflammation via the upregulation of several different genes involved in the inflammatory response, such as those that code for pro-inflammatory cytokines and adhesion molecules. This may occur by the activation of certain transcription factors, such as nuclear transcription factor κB (NF-κB), which is a ubiquitous transcription factor and pleiotropic regulator of numerous genes involved in immune and inflammatory responses. 5-ASA may protect mucosal tissue against oxidant-induced inflammation due to its ability to inhibit free radicals and NF-κB activation (and possibly other oxidant-sensitive transcription factors) (Conner and Grisham 1996).

Laboratory research has shown that 5-ASA has potent anti-oxidant activity, including free radical scavenging properties, the ability to degrade neutrophil-derived oxidants (e.g., hypochlorous acid), iron chelation, and the oxidation–reduction of it to a small amount. In addition, 5-ASA can inhibit the inflammatory responses induced by leukotrienes and prostaglandins by inhibiting the arachidonic acid metabolism (by inhibiting cyclooxygenase and lipoxygenase enzymes) (Abdu-Allah et al. 2016). Its high concentration has also been shown to inhibit certain functions of human neutrophils such as migration, degranulation, phagocytosis and superoxide anion formation. Therefore, it has been suggested that much of the anti-inflammatory activity of 5-ASA may be due to its numerous anti-oxidant properties (Yamada et al. 1990).

Recently, in an in vitro study, 5-ASA has been combined with cyanidin-3-glucoside to enhance its therapeutic effect. In this study, the combination of this anthocyanin with 5-ASA significantly increased the anti-inflammatory effect in a model of LPS-induced inflammation in a RAW 264.7 macrophage cell line. These results indicate that the effectiveness of the mixture is due to the synergistic interaction between the two compounds, which reduces the production of nitric oxide (NO) and ROS. In addition, part of the efficacy occurs by suppressing the translocation of activator protein-1 (AP-1) to the nucleus, thereby preventing p38 phosphorylation of MAPK and JNK (Pereira et al. 2019). Also, in further research on the anti-inflammatory activity of 5-ASA, it has been reported that combining it with chitosan

in an experimental study for 3 days caused an improvement in the anti-inflammatory effect of 5-ASA and also optimized its anti-inflammatory potential. This effect was greater for the chitosan–5-ASA compound than for 5-ASA alone in mice with experimental colitis, due to significant reductions in MPO, ALP, TNF-α, IL-6, IL-1, and NF-κB levels (Jhundoo et al. 2020).

Infiltrating macrophages and neutrophils are abundantly present in the inflamed gut of patients with IBD. These cells generate excess amounts of ROS and oxidants including HOCl, exceeding the intestinal anti-oxidant defense system, thus leading to an increase in oxidative stress and oxidant-mediated mucosal injury. Nuclear factor-erythroid 2 (NF-E2) p45-related factor 2 (Nrf2), a cytoprotective transcription factor against oxidative stress, is sequestered in the cytoplasm by association with Kelch-like ECH-associated protein 1 (Keap1), resulting in enhanced proteosomal degradation of Nrf2. Under oxidative stress, Nrf2 is released from Keap1, either by direct oxidative modification of Keap1 or after phosphorylation by redox-sensitive protein kinases. It translocates to the nucleus and, in combination with other transcription factors, activates the gene transcription of a battery of anti-oxidative enzymes, resulting in a cytoprotective adaptive response. These anti-oxidative enzymes have been shown to attenuate inflammatory damage and to neutralize ROS implicated in inflammatory signaling pathways. This study showed that 5-ASA is oxidized by HOCl under oxidative stress conditions and converted to iminoquinone and quinone which have electrophilic properties. Under these conditions, the binding between Nrf2 and Keap1 is weakened, and the tendency of Keap1 to oxidize 5-ASA increases, thus causing Keap1 to separate from Nrf2 and bind to the oxidized 5-ASA. Nrf2 is released, activated, and transported to the nucleus, which then induces the expression of anti-oxidant enzymes, including heme oxygenase (OH)-1. This enzyme has special anti-inflammatory properties and reduces inflammation in vitro and in vivo (Fig. 2) (Kang et al. 2017).

Antibacterial and antifungal activity

In patients with UC, high concentrations of 5-ASA reduce pathogenic bacteria, such as proteobacteria, and increase some beneficial bacteria, such as faecalibacterium. Previous studies also suggest that 5-ASA may have a positive effect on the intestinal mucosal microflora so that it can correct dysbiosis in patients with UC (Olaisen et al. 2019). The reason for this is that 5-ASA may reduce the persistence in inflamed mucosa by reducing the level of polyphosphate in various

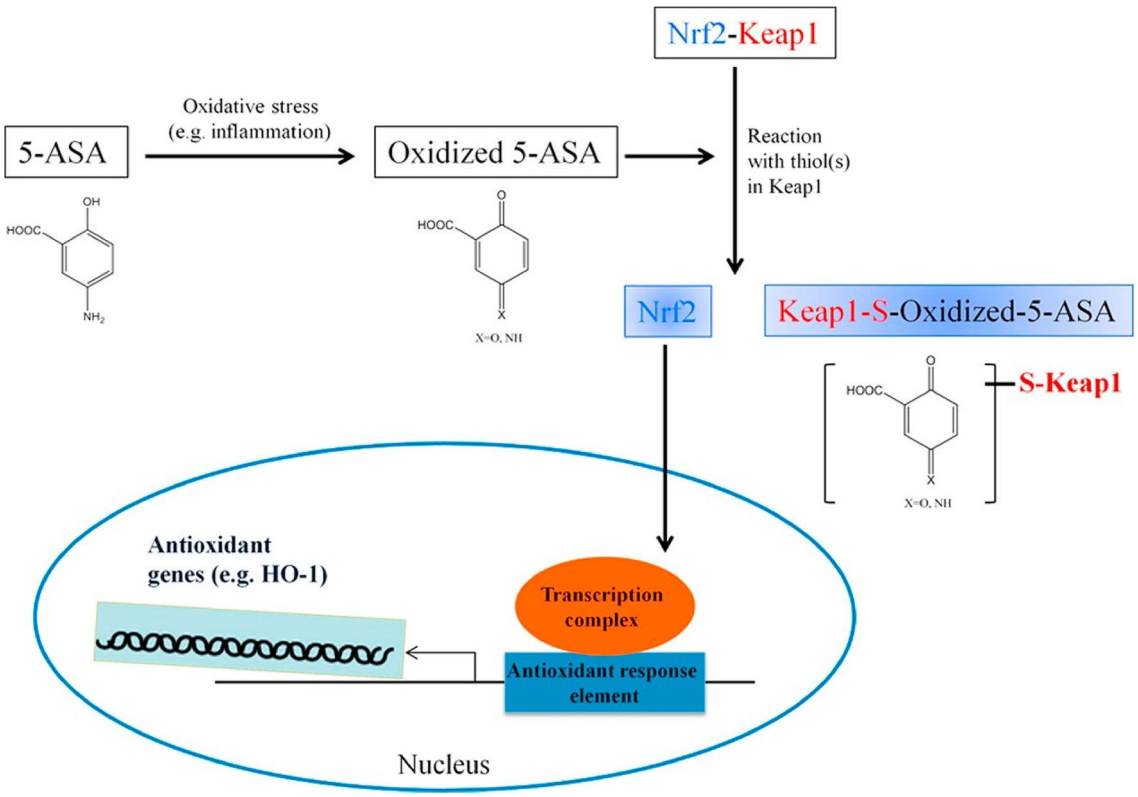

Fig. 2 Activation of the Nrf2-HO-1 pathway by covalent binding of oxidized 5-aminosalicylic acid to Keap1 (Kang et al. 2017)

pathogenic bacteria (Buchner and Lichtenstein 2019). In addition, in an investigation of the bacterial profile of feces in 12 patients with irritable bowel syndrome (IBS) has been reported that treatment with 5-ASA reduced fecal bacteria by 46%, leading to greater balance and improved symptoms in patients with IBS (Andrews et al. 2011).

Previous research has shown 5-ASA antibacterial activity, with *E. coli* involved in the pathogenesis of Crohn's disease, in that its adhesive strains in the mucosa can attack colon polyps and cancers, leading to activating toll-like receptors, TNF, IL-8, and NF-κB signaling. On the other hand, 5-ASA in a dose-dependent manner can prevent the release of MAPK-dependent IL-8 produced by *E. coli* strains. Also, in a study on the expression of bacterial genes, it has been reported that 5-ASA leads to the downregulation of the expression of genes that are involved in bacterial invasion, but its mechanism has not been properly elucidated (Kaufman et al. 2009). Research has shown that functionalized silver nanoparticles with 5-ASA have a bacteriostatic effect in vitro against *E. coli* and *S. aureus* in a time- and concentration-dependent manner, and that this antibacterial property of the particles is maintained for a long time. However, these synthesized nanoparticles did not show an inhibitory effect on *C. albicans* yeast (Lazić et al. 2018).

Studies have shown that 5-ASA metal complexes (Fig. 3) have more antibacterial activity against bacteria (*S. aureus*, *E. coli*, *P. aeruginosa*, and *B. subtilis*) in vitro than the parent 5-ASA. On the other hand, it has been stated that metal complexes are more potent in inhibiting the growth of micro-organisms than ligands against similar micro-organisms under similar experimental conditions. This may be due to the change in structure due to coordination and chelating trends making metal complexes act as more powerful and potent bacteriostatic agents, thus inhibiting the growth of the micro-organisms. In addition, in these studies antifungal properties of 5-ASA and its metal complexes have been reported using the in vitro diffusion method. The results of these studies show that 5-ASA metal complexes have a greater antifungal effect against *Candida albicans* and *Aspergillus fumigatus* than 5-ASA itself. The increase in the antifungal activity of the metal complexes inhibits multiplication process of the microbes by blocking their active sites. Such increased activity on metal chelation can be explained on the basis of the Tweedy chelation theory, which states that chelation increases the nature of lipophilicity due to the interaction between metal ions and lipids. This may lead to the failure of the cell's permeability barrier, resulting in interference with the cell's natural process (Soliman and Mohamed 2013).

Anticancer activity

Colorectal cancer (CRC) is one of the most common and malignant cancers in the world today and may occur due to abnormal growth in UC in patients. 5-ASA as a promising candidate for chemoprevention of CRC through COX-dependent (inflammatory) and COX-independent (non-inflammatory) mechanisms, epidermal growth factor receptor (EGFR) inhibition, NF-κB, and Wnt/β-catenin signaling, while PPAR-γ activation fights CRC cells (Stolfi et al. 2013; Allgayer 2003). Research has shown that, in patients with CRC, the use of 5-ASA for 14 days selectively induces apoptosis in tumor cells (Krieken 1999). In addition, a 40-mM dose of 5-ASA significantly reduces the expression of mRNA and c-Myc protein in CRC cells and induces apoptosis in them (Chu et al. 2007).

Previous studies have shown that 5-ASA from EGFR, a tyrosine kinase of membrane that induces mitogenic signaling in CRC cells, prevents it. Furthermore, 5-ASA affects the Wnt/β-catenin pathway in CRC cells by inhibiting phosphatase A_2 and degrading β-catenin. 5-ASA also reduces colorectal inflammation and cancer by interacting with and increasing PPAR-γ expression and activation. 5-ASA can also inhibit COX-2 at the level of RNA and protein, which is associated with a significant reduction in prostaglandin E2 (PGE2) synthesis, growth retardation, and an increase in CRC cells. However, exogenous PGE2 does not reverse the 5-ASA-mediated CRC cell proliferation block. 5-ASA also inhibits the growth of DLD-1, a COX-deficient CRC cell line, thus suggesting that the anti-proliferative effect of 5-ASA on CRC cells is not strictly dependent on the inhibition of COX-2/PGE2 (Stolfi et al. 2008).

Studies have reported that 5-ASA suppresses the growth of HT-29 cell line as a type of CRC cell and is able to inhibit the expression of matrix metalloproteinases (MMPs) through NF-κB-mediated and invasive cellular signals (Kim et al.

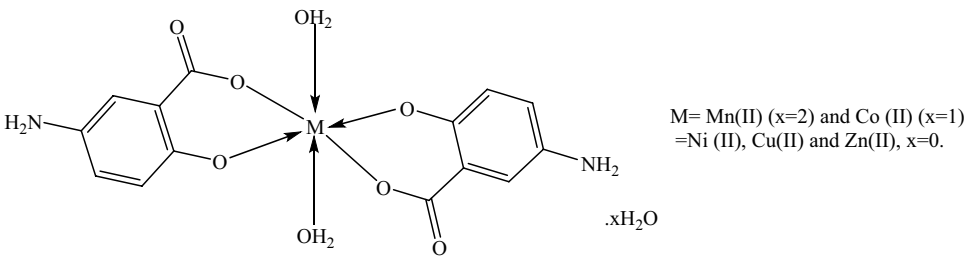

Fig. 3 Structure of 5-ASA metal complexes

2009). It is noteworthy that 5-ASA inhibits the progression of colitis-associated CRC but has no effect on sporadic CRC in the FabplCre;Apc$^{15lox/+}$ mice model (Koelink et al. 2009).

Subsequent research has shown that 5-ASA inhibits the signaling pathway of β-catenin through a protein called μ-protocadherin, which belongs to the cadherin family, by isolating β-catenin from the plasma membrane of treated cells. This inhibition process is controlled by disruption of the cell cycle and is transcriptional (Parenti et al. 2010).

According to the mentioned studies, the results show that the use of 5-aminosalicylate is associated with a reduced risk of colorectal neoplasia in patients with UC, especially in cases where there is an average daily dose of 5-aminosalicylate (Zhao et al. 2014). Meanwhile, 5-ASA can suppress the cancer stem phenotype in adenoma-derived cells. For this reason, as a cost-effective and tolerable option, 5-ASA is a prominent candidate for reducing the risk of colorectal polyps and CRC in high-risk individuals (Dixon et al. 2021).

Anti-amyloid activity

More than 20 human diseases, including Alzheimer's, type 2 diabetes, Parkinson's disease, Huntington's, Creutzfeldt–Jakob's disease, etc. with protein aggregation and precipitation, with aggregates adopting either highly ordered (amyloid fibril) or disordered (amorphous) forms, are related. During these events, the normally folded soluble proteins form misfolding intermediate structures and accumulate in the form of insoluble extracellular protein deposits, leading to cell damage and organ dysfunction. The formation of amyloid fibrils is not limited to disease-related proteins. Many other proteins also have the potential to form amyloid aggregates under laboratory conditions under partial denaturation (Hatamvand et al. 2020).

A study of fibrillation and defibrillation of lysozyme amyloid fibrils in vitro has shown that 5-ASA in a 1:1 ratio with lysozyme protein had a potent inhibitory effect on protein fibrillation, confirmed by tests with Congo red absorbance, circular dichroism spectroscopy, thioflavin T fluorescence assay, 1-anilinonaphthalene-8-sulfonic acid fluorescence, and field-emission scanning electron microscopy. Therefore, 5-ASA can be important as a drug to prevent the development of hereditary lysozyme amyloidosis and other non-neuropathic hereditary amyloidosis (Faramarzian et al. 2020). A recent study on the interaction of 5-ASA with insulin in vitro has shown that 5-ASA could be considered as a golden switch for inhibiting the formation of amyloid accumulations of insulin protein in these conditions (Bardineshin 2021).

Gastric protection activity

Various medicinal compounds with various mechanisms have been used over time to protect the stomach (Beiranvand and Beiranvand 2021). For example, previous studies have shown that SSZ can prevent ethanolic gastric ulcers. Regarding its mechanism of action, SSZ appears to inhibit some inflammatory responses by inhibiting gastric lipoxygenase activity and the production of leukotriene C_4. It also protects the stomach against ethanol-induced stress by increasing mucus in the stomach and by the rapid emptying of gastric contents (Cho et al. 1987). Similarly, 5-ASA protects rats from ischemic-/reperfusion-induced gastric bleeding by removing the hydroxyl radicals produced by ischemic reperfusion and reducing vascular lesions in experimental models (Kvietys et al. 1988). Interestingly, some investigations have also suggested a 5-ASA mechanism in the inhibition of stress-induced gastric ulcers, the inhibition of lipoxygenase activity, and leukotriene C_4 synthase (Garg et al. 1990). Recently, in a study on the protective and anti-oxidant effects of 5-ASA it has been reported that pre-treatment of rats at doses of 50 and 100 mg/kg 5-ASA caused reduced oxidative stress and free radical scavenging of ethanol-induction by decreasing levels of ROS, MDA, and carbonyl protein. In addition, 5-ASA can cause strengthening of the anti-oxidant defense system of gastric mucosal cells in a dose-dependent manner and prevent tissue damage by increasing glutathione (GSH) levels and catalase activity (Beiranvand and Bahramikia 2020; Beiranvand 2020).

Anti-diverticulosis activity

Studies have reported that 5-ASA was administered at doses of 400 and 800 mg in two similar studies for different periods of time in patients with symptomatic diverticular. Patients treated with 5-ASA had the lowest global symptomatic score in two studies compared to those treated with rifaximin (standard drug). At the end of this study, it has been found that 5-ASA was as effective in reducing some symptoms as rifaximin in relieving the symptoms of diverticular disease, and some symptoms disappeared completely with a dose of 800 mg of 5-ASA (Di Mario et al. 2005; Comparato et al. 2007). Also, administration of 5-ASA at a dose of 1.6 g per day in patients affected by recurrent attacks of diverticular disease has shown that daily use of 5-ASA for 24 months is effective in preventing its recurrence. Interestingly, this administration of 5-ASA confirmed the hypothesis that patients with recurrent attacks of diverticulosis have severe inflammation in the mucosa of their large intestine

(Tursi et al. 2007). In addition, at a clinical trial controlled by placebo, it was reported that administration of 5-ASA at a dose of 1000 mg three times/daily reduced and relieved pain in patients prone to flare-up of diverticular disease symptoms (Kruis et al. 2013).

Treatment of inflammatory bowel disease

IBD is a term used to describe disorders including chronic inflammation of the gastrointestinal tract, which includes UC and Crohn's disease. UC is an idiopathic recurrent inflammatory disease characterized by persistent inflammation in the intestinal mucosa or lamina propria, starting in the rectum and potentially involving the entire large intestine. Although the etiology of UC remains unclear, it is generally hypothesized to be a multifactorial condition induced by a combination of genetic, environment and gut microbiota, which triggers the luminal mucosa, leading to an exaggerated and inappropriate immune response, which plays an important role in the initiation, augmentation, and perpetuation of UC. Loss of immune tolerance leads to inflammation induced by increases in various pro-inflammatory mediators secreted from different cell types. They stimulate proliferation of antigen-specific effectors in order to trigger the adaptive immune system and lead to local and systemic inflammation. Cytokines play major roles in inflammatory processes as cell-signaling molecules driving inflammation and UC pathogenesis via different roles, such as production of inflammatory mediators and activation of inflammatory pathways. As a consequence, cytokines are directly responsible for epithelial injury, intestinal barrier defects, and tissue damage, because they are involved in various biological processes, cell activation, and differentiation, and are central factors in the development of inflammatory and immune response.

The pro-inflammatory cytokines., TNF-α, IL-1, and IL-6, play a major role in UC and serve as significant signals in the increase and persistence of UC. They are directly responsible for mucosal and tissue damage, and thus stimulate certain disease-specific immune responses in UC. TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation, and is involved in inflammation, apoptosis, lymphocyte stimulation, and activation of immune cell functions. TNF-α activates macrophages and lymphocytes, stimulates B cells, and increases IFN-γ production by T cells. In addition, TNF-α activates mitogen-activated protein kinase and nuclear factor (NF)-κB pathways, which contribute to cell differentiation, cell proliferation, and upregulation of pro-inflammatory cytokines. Thus, an increase in TNF-α expression might cause defects in mucosal barrier function in patients with UC, exacerbating inflammation. IL-1 is produced from macrophages and possesses regulatory and pro-inflammatory functions in the pathogenesis of UC. IL-1 mainly produces IL-1α and IL-1β, which induce cyclooxygenase type 2, inducible nitric oxide synthase, and phospholipase A. IL-1 receptor antagonist (IL-1Ra) plays a role as a mechanism controller. UC patients show high levels of IL-1Ra and high IL-1Ra/IL-1 ratios with increasing IBD activity. Thus, IL-1Ra might be a part of the inflammatory downregulatory mechanism. An increase in IL-1β in IBD possibly results from the stimulation of macrophages that activate IL-1β-converting enzyme, and thereby releases mature IL-1β into the colonic mucosa. IL-6, too, is a typical pro-inflammatory cytokine mainly produced from macrophages and secreted during the acute phase of the inflammatory response. In UC patients, an increase in IL-6 has been observed in serum and tissue biopsies (Tatiya-Aphiradee et al. 2019; Kaur and Goggolidou 2020; Roda et al. 2011).

Many in vivo studies have shown that 5-ASA is able to improve and treat UC (Hayashi et al. 2009) and Crohn's disease (Simon et al. 2017) as IBDs. In some of these studies, it has been suggested that the administration of 2 ml of 5-ASA once daily through enemas for 1 week in rats with colitis can reduce the penetration of inflammatory cells and prevent experimental colitis by reducing NO, MDA, and MPO activity (Aslan et al. 2007). In addition to receiving 100 mg/kg 5-ASA in experimental rats, by reducing interleukin IL-1β, IL-6, and TNF-α and increasing the activity of glutathione peroxidase (GPx), GSH, SOD, and total anti-oxidant capacity showed that it reduces stress oxidative, secretion of pro-inflammatory cytokines, the destruction of colon tissue, and strengthens the endogenous anti-oxidant defense system through its anti-oxidant and anti-inflammatory properties (Rezaei et al. 2019). It has also been reported that rats treated with a dose of 20 mg/kg 5-ASA, due to anti-oxidant activity, showed a reduction in lipid peroxidation, and a decrease in the expression of iNOS and NF-κB, by increasing the pressure of the anal sphincter. This also reduces the production of pro-inflammatory cytokines (including IL-1, -6, and -8) and free radicals derived from acetic acid in experimental colitis (Moura et al. 2016). In addition, it has been shown that part of the anti-inflammatory activity of 5-ASA is due to the suppression of phosphorylation of JNK and p38 proteins in mouse macrophage cells (Qu et al. 2017).

Research has shown that the combination of crocin and 5-ASA has a synergistic effect against UC. However, doses of 100 and 300 mg/kg 5-ASA were more effective in improving macroscopic and microscopic tissue damage in UC by increasing SOD activity and decreasing MDA and TNF-α levels in a dose-dependent manner (Faramarzpour et al. 2019). It is noteworthy that 5-ASA in inflammatory bowel patients improves ulcers occurring in intestinal epithelial cells by repairing cellular anchoring complexes and the membranous localization of junctional proteins, affecting cellular aging, cell cycle distribution, and cells restricted

in phases G1 or S, without causing apoptosis (Khare et al. 2019).

An in vitro study has shown that 5-ASA stimulates the healing of intestinal epithelial ulcers in such a way that a dose of 100 mg/ml 5-ASA has a significant effect on the migration and proliferation of a class of small intestinal cells, called IEC-6. It has also been shown that the anti-inflammatory effect of 5-ASA is independent of TGF-β and that it has no toxic or apoptotic effects on IEC-6 (Baumgart et al. 2005).

Interestingly, a number of studies have shown that binding of 5-ASA to another molecule can enhance its anticolitis effects. In one study, the combination of 5-ASA with amisulpride (ASP) via the azo bond (ASP-azo-ASA) created a colon-specific drug. When it was given to rats with colitis, colonic inflammation induced by 2,4-dinitrobenzene sulfonic acid was reduced more effectively (Kim et al. 2019). It has also been shown that binding of 5-ASA by azo bonding to compounds other than sulfapyridine, including ρ-aminobenzoic acid, ρ-aminophenol, and salicyl aldehyde, increases its anti-inflammatory and anti-edema activity and protects the colon against colitis. Among the mentioned compounds, the binding of salicyl aldehyde to 5-ASA can further increase the anti-inflammatory and anti-edematous effects of 5-ASA (Garjani et al. 2004).

Clinical trials have also shown that 5-ASA has a higher therapeutic effect than SSZ in the treatment and prevention of colitis (Greinwald 2000) and Crohn's disease (Caprilli et al. 1994), and, at higher doses (2.4 g/day) can be more effective than SSZ (Riley et al. 1988).

Other pharmacological activity

Studies have shown that 5-ASA protects the kidneys from acute ischemia–reperfusion damage by decreasing serum NO and creatinine levels and increasing urinary creatinine. It is believed that administration of 5-ASA at a dose of 300 mg/kg prior to ischemia in rats prevents through its anti-oxidant activity the formation of peroxynitrite by removing superoxide, hydroxyl, and RNS from re-ischemia. 5-ASA, with increases glomerular filtration rate in the kidney, also improves its function and minimizes the severity of histopathological changes in the kidney (Banaei 2016). In addition, there is evidence that 5-ASA is useful in the treatment of rheumatoid arthritis (Smedegård and Björk 1995). Research has also shown that taking 800 mg of 5-ASA three times a day for 8 weeks reduces inflammation in the affected area by reducing the penetration of immune cells in the colon. Also, by activating peroxisome proliferator-activated receptors, it repairs intestinal epithelial ulcers in patients with IBS (Corinaldesi et al. 2009; Cheng et al. 2020).

Administration of 5-ASA at a dose of 50 mg for 8 weeks in patients with psoriasis has been reported to improve these patients as well as significantly reduce the thickness and size of the psoriasis plaques and erythema (Bharti 1996). In addition, research has shown that oral doses of 50 and 100 mg/kg 5-ASA in rats weighing 180–200 g can be effective in the prevention and treatment of liver fibrosis. 5-ASA shows signs of liver improvement by lowering serum levels of AST, ALT, and total bilirubin. It also prevents oxidative stress by maintaining SOD levels and GSH and decreasing tissue MDA levels, and reduces the severity of fibrotic damage by suppressing TNF-α and regulating the signaling pathways of TGF-β1, α-SMA, and caspase-3 (Ramadan et al. 2018).

Safety

Aminosalicylates have the best safety profile of all medical therapies currently used in IBD. Minor but common side effects of 5-ASA include headache, nausea, dyspepsia, flatulence, diarrhea, abdominal pain, and rash. Rare but serious side effects include febrile neutropenia (Moro-Agud 2018), pleuritis, pericarditis, myocarditis, pancreatitis, and cholestatic hepatitis. Rare cases of interstitial nephritis have been reported mainly when using high doses of 5-ASA formulations. Also, when 5-ASA is combined with SP in SSZ, the side effects are mainly related to the sulfa moiety (Williams et al. 2011; Scholar 2009). Recently as well some unpublished data suggest that intragastric administration of 5-ASA at doses greater than 100 mg/kg in rats weighing approximately 200 g does not protect their stomachs from ethanolic damage.

Conclusions and future perspectives

Considering that, in most of the diseases mentioned in this review article, oxidative stress and free radicals directly and indirectly play a role, I believe that 5-ASA's beneficial effects are due to its anti-inflammatory and anti-oxidant activities directly (by eliminating free radicals) and indirectly (by increasing the expression of anti-oxidant genes) and that it has the ability to act as a successful drug molecule. On the other hand, the development of drugs requires years of in vivo and in vitro clinical studies. In this regard, many studies on 5-ASA have been conducted during recent years, the expression of which provides the basis for a better cognition of this drug. Recent research findings show that 5-ASA is a molecule with high therapeutic potential that, if a suitable dose is discovered for various diseases, can have a wide range of pharmacological effects. However, studies have shown that further chemical structure changes and optimization of this small molecule can increase its biological and pharmacological activities. It can also cause improvements in pharmacokinetics, reduce side effects, detect other

drug activities, and increase its safety. Finally, I hope this study can be useful in understanding the other medicinal values of this synthetic anti-oxidant and finding ways to better understand them.

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Declarations

Conflict of interest The author declares that he has no competing interests.

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