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**Treatment repurposing for inflammatory bowel disease using literature-related discovery and innovation**

Kostoff RN *et al*. Treatment repurposing for IBD

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**Abstract**

Inflammatory bowel disease (IBD) incidence has been increasing steadily, most dramatically in the Western developed countries. Treatment often includes lifelong immunosuppressive therapy and surgery. There is a critical need to reduce the burden of IBD and to discover medical therapies with better efficacy and fewer potential side-effects. Repurposing of treatments originally studied in other diseases with similar pathogenesis is less costly and time intensive than de novo drug discovery. This study used a treatment repurposing methodology, the literature-related discovery and innovation (LRDI) text mining system, to identify potential treatments (developed for non-IBD diseases) with sufficient promise for extrapolation to treatment of IBD. By searching for desirable patterns of twenty key biomarkers relevant to IBD (*e.g.*, inflammation, reactive oxygen species, autophagy, barrier function), the LRDI-based query retrieved approximately 9500 records from Medline. The most recent 350 records were further analyzed for proof-of-concept. Approximately 18% (64/350) met the criteria for discovery (not previously studied in IBD human or animal models) and relevance for application to IBD treatment. Many of the treatments were compounds derived from herbal remedies, and the majority of treatments were being studied in cancer, diabetes, and central nervous system disease, such as depression and dementia. As further validation of the search strategy, the query identified ten treatments that have just recently begun testing in IBD models in the last three years. Literature-related discovery and innovation text mining contains a unique search strategy with tremendous potential to identify treatments for repurposing. A more comprehensive query with additional key biomarkers would have retrieved many thousands more records, further increasing the yield of IBD treatment repurposing discovery.

**Key words:** Treatment repurposing; Treatment repositioning; Inflammatory bowel disease; Literature-based discovery; Text mining; Crohn’s disease; Ulcerative colitis; Novel treatments

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**Core tip:** A text-mining approach was used to identify treatments from non-inflammatory bowel disease (IBD) diseases that could be extrapolated to treat IBD. Sixty-four treatment concepts were identified in different phases of development, ranging from laboratory research to clinical application. Many more were possible with a longer and well-resourced study. Ten of the non-IBD concepts that were excluded from being classified as discovery would have been classified as discovery if the study had been conducted in 2016. Thus, this approach has the capability to identify/predict many new areas of research for treating IBD.

**INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal (GI) tract characterized by alternating phases of relapse and remission, clinically defined into two major subtypes: Crohn’s disease (CD) and ulcerative colitis (UC)[1]. Globally, the incidence of IBD is increasing, especially among newly industrialized countries where IBD was previously non-existent[2]. Childhood onset of IBD is also increasing in a similar pattern globally, suggesting evolving environmental risk factors[3].

In 2017, there were 6.8 million cases of IBD globally. The age-standardized prevalence rate increased from 79.5 per 100000 population in 1990 to 84.3 per 100000 population in 2017. At the regional level of global burden of disease (GBD), the highest age-standardized prevalence rate in 2017 occurred in North America (422.0 per 100000) and the lowest age-standardized prevalence rates were observed in the Caribbean (6.7 per 100000 population). High sociodemographic index (SDI) locations had the highest age-standardized prevalence rate, while low SDI regions had the lowest age-standardized prevalence rate[4].

The pathogenesis of IBD is multifactorial, which makes prevention and treatment of IBD challenging. Genetic predisposition contributes to dysregulation of both innate and adaptive immunity[5]. Environmental triggers (diet, infection, antibiotics, and toxin exposure) affect the intestinal microbiome and influence epigenetic changes that alter immune regulation[6]. Treatment, particularly in those with more aggressive disease, is generally lifelong, and often includes immunosuppressive therapy and surgery. There is a critical need to both (1) identify and eliminate contributing factors to disease to reduce the burden of IBD; and (2) discover novel medical therapies that provide better efficacy with fewer potential side-effects.

**POTENTIAL IBD TREATMENT DISCOVERY**

The standard approach to drug discovery is costly and time intensive. Repurposing treatments (1) already being developed; or (2) in clinical application for other conditions with overlapping pathogenesis is an attractive alternative to *de novo* drug discovery. This repurposing approach involves extrapolating a treatment developed for a non-IBD disease, such as rheumatoid arthritis, for use in IBD. Many of the upfront develop costs can be avoided and some safety data already exists. However, given the vastness of the current published biomedical literature, quickly identifying potential novel treatments for IBD remains challenging.

A unique methodology to facilitate treatment repurposing has been developed by the first author using a literature-related discovery and innovation (LRDI) text-mining approach[7]. This approach involves matching patterns of biomarker changes (tests that measure a normal biologic, a pathologic process, a response to treatment, or predict a response[8]) in the disease-of-interest core literature with similar pattern changes in the remainder of the biomedical literature. The objective of this study is to use the LRDI approach to identify potential novel treatments for IBD that cannot be found in the IBD core literature.

However, the simultaneous removal of contributing factors to disease pathogenesis is equally important to treatment. A protocol (that includes identification and removal of contributing factors) to prevent and reverse chronic diseases is described in Appendix 1, along with examples of contributing factors associated with IBD. Contributing factors as used in the present study are, in theory, modifiable (reduced or eliminated through personal choice and/or government regulation), and can be broadly categorized as Lifestyle, Iatrogenic, Biotoxins, Occupational/Environmental, PsychoSocial/SocioEconomic. They include smoking, excessive alcohol, pesticides, wireless radiation, ionizing radiation, brominated flame retardants, *etc*[9].

**METHODOLOGY**

The specific details of LRDI-based treatment repurposing steps are contained in Appendix 2, as are the specific search terms used in the query. The query was executed April 19, 2020.

Figure 1 shows the flow diagram of the treatment discovery/repurposing process. Briefly, key biomarkers and their direction of change in the existing IBD literature were identified from examination of a large number of existing IBD treatments in all phases of development and clinical application (the reasons for identifying/using the large numbers of existing treatments are discussed in more detail in Appendix 3). These biomarkers and their desired treatment-derived directions of change are combined to form a query. The query was then used to search the non-IBD literature in Medline for potential treatments whose effects on biomarker changes were similar to those from existing IBD treatments in the core IBD literature (*i.e.*, similar biomarker “signatures”). Those potential treatments from the non-IBD Medline literature that could not be found in the core IBD Medline literature were considered to be discovery.

Once the biomarkers associated with IBD were identified, they were ranked by (1) prevalence in the literature; and (2) clinical relevance. From hundreds of potential biomarkers, the top twenty (and variants) were prioritized and, along with their treatment-derived directions of change, were used in the treatment discovery query. Biomarkers from multiple pathways known to be associated with the inflammatory/immune response in IBD (*i.e.*, cytokines, reactive oxygen species, autophagy and barrier function markers) were selected. All combinations of two biomarkers were then used to define the pattern for matching (*e.g.*, decrease CRP AND increase IL-10). Categorical phrases, such as “anti-inflammatory” were also used as a biomarker term. The resultant query was entered into the Web of Science search engine for Medline.

In a proof-of-concept model, the 350 most recent records from 9500 records retrieved were analyzed further to (1) demonstrate the potential power of the technique; and (2) provide useful results to the IBD community as well. These potential treatments were then validated independently to assess applicability to IBD, in order to ensure the treatment was not already being tested in IBD models.

**RESULTS**

The treatments identified in this study include both (1) potential novel IBD treatments (Table 1)[10-73]; and (2) examples of recently studied IBD treatments that would have also been identified as potential novel treatments had this study been performed in 2016 (Table 2)[74-95]. The latter reflect the predictive nature of the LRDI treatment repurposing technique.

Table 1 contains the potential novel IBD treatments. The leftmost column contains the novel treatment and alternative name(s); the center column contains the biomarkers that were assessed in the reported study and that changed in the desired existing IBD treatment-derived directions; the rightmost column contains the reported study reference.

Table 2 shows examples of recent studies that would have been captured as novel treatments had the study/query been performed in 2016. These results reflect the predictive nature of the LRDI-based treatment repurposing methodology. The leftmost column contains the treatment and alternate name(s); the next column contains the biomarkers that were (1) assessed in the reported study; and that (2) changed in the desired treatment-derived direction; the final two columns reflect (1) the non-IBD application(s) of the treatment prior to 2016 (R1); and 2) the post-2016 evaluation of the potential treatment for IBD application (R2).

**DISCUSSION OF RESULTS**

The potential IBD treatments were derived from a wide swath of categories, including treatments for diabetes, cancer, and central nervous system disease, such as depression and dementia. Many of the compounds are derived from herbal remedies. Most are in the laboratory test phase, although many of these and their parent compounds have been in medical use for diseases other than the projected application represented by the paper cited. There is more emphasis on plant-based compounds and their derivatives than standard commercial synthetic drugs. This is to be expected, since the pharmaceutical companies who develop these drugs have substantial resources to devote towards searching for other applications for drugs under patent coverage with established manufacturing techniques.

Much of the research on plant-based treatments tends to be conducted by researchers indigenous to where these plants are most plentiful. They would not be expected to have the resources available to devote towards searching for the full spectrum of applications that the pharmaceutical companies have. Therefore, more targets of opportunity for treatment discovery exist in these non-mainline categories, as reflected in the results presented in this paper. It should be emphasized these drug/non-drug conclusions are based on results obtained using twenty selected biomarkers, out of a potential pool of hundreds of biomarkers. It is unknown whether the use of other available biomarkers for the discovery query would have generated novel treatments with a different drug/non-drug balance.

Approximately eighteen percent of the 350 records examined could be categorized as potential novel treatments for repurposing. Many of the records excluded from discovery consideration were done so on the basis of one or two prior recent records (published in 2017-2020) containing the same treatment applied to IBD (human or animal studies).

Thus, had this study been done four-five years ago, using the same query, those studies would have been identified as a potential novel treatment discovery. This is confirmation of the predictive power of the present technique for use as a repurposing approach.

**CONCLUSION**

Potential novel IBD treatments have been identified using a powerful text mining approach that identifies pattern changes of clinically relevant biomarkers being studied in non-IBD populations. Approximately 64 potential novel IBD treatments were identified in this proof-of-concept model, but many more were possible from an expanded study. Additionally, the predictive power of the approach for identifying future treatments that would be pursued through laboratory research was confirmed, showing the value of this approach for identifying and expanding relevant fields of research.

**REFERENCES**

1 **Ahluwalia B**, Moraes L, Magnusson MK, Öhman L. Immunopathogenesis of inflammatory bowel disease and mechanisms of biological therapies. *Scand J Gastroenterol* 2018; **53**: 379-389 [PMID: 29523023 DOI: 10.1080/00365521.2018.1447597]

2 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/s0140-6736(17)32448-0]

3 **Sýkora J**, PomahaÄová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* 2018; **24**: 2741-2763 [PMID: 29991879 DOI: 10.3748/wjg.v24.i25.2741]

4 **GBD 2017 Inflammatory Bowel Disease Collaborators.** The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 17-30 [PMID: 31648971 DOI: 10.1016/s2468-1253(19)30333-4]

5 **Kim DH**, Cheon JH. Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies. *Immune Netw* 2017; **17**: 25-40 [PMID: 28261018 DOI: 10.4110/in.2017.17.1.25]

6 **Rogler G**, Biedermann L, Scharl M. New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways. *Swiss Med Wkly* 2018; **148**: w14599 [PMID: 29566254 DOI: 10.4414/smw.2018.14599]

7 **Kostoff RN**. Treatment Repurposing using Literature-related Discovery. *J* *Scientometric Res* 2019; **8**: S74-S84 [DOI: 10.5530/jscires.8.2.25]

8 **Biomarkers Definitions Working Group.** Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001; **69**: 89-95 [PMID: 11240971 DOI: 10.1067/mcp.2001.113989]

9 **Kostoff RN**. Prevention and reversal of chronic disease: lessons learned. Georgia Institute of Technology. 2019. Available from: <http://hdl.handle.net/1853/62019>

10 **Maehara T**, Fujimori K. Contribution of FP receptors in M1 macrophage polarization via IL-10-regulated nuclear translocation of NF-κB p65. *Biochim Biophys Acta Mol Cell Biol Lipids* 2020; **1865**: 158654 [PMID: 32036038 DOI: 10.1016/j.bbalip.2020.158654]

11 **Ma Q**, Huang W, Zhao J, Yang Z. Liu Shen Wan inhibits influenza a virus and excessive virus-induced inflammatory response via suppression of TLR4/NF-κB signaling pathway *in vitro* and in vivo. *J Ethnopharmacol* 2020; **252**: 112584 [PMID: 31972325 DOI: 10.1016/j.jep.2020.112584]

12 **Xi Y**, Huang X, Tan G, Chu X, Zhang R, Ma X, Ni B, You H. Protective effects of Erdosteine on interleukin-1β-stimulated inflammation via inhibiting the activation of MAPK, NF-κB, and Wnt/β-catenin signaling pathways in rat osteoarthritis. *Eur J Pharmacol* 2020; **873**: 172925 [PMID: 31958453 DOI: 10.1016/j.ejphar.2020.172925]

13 **Tian F**, Wang Z, He J, Zhang Z, Tan N. 4-Octyl itaconate protects against renal fibrosis via inhibiting TGF-β/Smad pathway, autophagy and reducing generation of reactive oxygen species. *Eur J Pharmacol* 2020; **873**: 172989 [PMID: 32032597 DOI: 10.1016/j.ejphar.2020.172989]

14 **Mozaffarnia S**, Teimuri-Mofrad R, Rashidi MR. Design, synthesis and biological evaluation of 2,3-dihydro-5,6-dimethoxy-1H-inden-1-one and piperazinium salt hybrid derivatives as hAChE and hBuChE enzyme inhibitors. *Eur J Med Chem* 2020; **191**: 112140 [PMID: 32088494 DOI: 10.1016/j.ejmech.2020.112140]

15 **Liu K**, Tian LX, Tang X, Wang J, Tang WQ, Ma ZF, Chen T, Liang HP. Neutrophilic granule protein (NGP) attenuates lipopolysaccharide-induced inflammatory responses and enhances phagocytosis of bacteria by macrophages. *Cytokine* 2020; **128**: 155001 [PMID: 32035329 DOI: 10.1016/j.cyto.2020.155001]

16 **Zhou J**, Xi Y, Zhang J, Tang J, Zhou X, Chen J, Nie C, Zhu Z, Ma B. Protective effect of Dioscorea zingiberensis ethanol extract on the disruption of blood-testes barrier in high-fat diet/streptozotocin-induced diabetic mice by upregulating ZO-1 and Nrf2. *Andrologia* 2020; **52**: e13508 [PMID: 31957918 DOI: 10.1111/and.13508]

17 **Xiao J**, Yao R, Xu B, Wen H, Zhong J, Li D, Zhou Z, Xu J, Wang H. Inhibition of PDE4 Attenuates TNF-α-Triggered Cell Death Through Suppressing NF-κB and JNK Activation in HT-22 Neuronal Cells. *Cell Mol Neurobiol* 2020; **40**: 421-435 [PMID: 31659561 DOI: 10.1007/s10571-019-00745-w]

18 **Pandey SN**, Kwatra M, Dwivedi DK, Choubey P, Lahkar M, Jangra A. 7,8-Dihydroxyflavone alleviated the high-fat diet and alcohol-induced memory impairment: behavioral, biochemical and molecular evidence. *Psychopharmacology (Berl)* 2020; **237**: 1827-1840 [PMID: 32206827 DOI: 10.1007/s00213-020-05502-2]

19 **Shenoda BB**, Ramanathan S, Gupta R, Tian Y, Jean-Toussaint R, Alexander GM, Addya S, Somarowthu S, Sacan A, Ajit SK. Xist attenuates acute inflammatory response by female cells. *Cell Mol Life Sci* 2020 [PMID: 32193609 DOI: 10.1007/s00018-020-03500-3]

20 **Perrotta P**, Van der Veken B, Van Der Veken P, Pintelon I, Roosens L, Adriaenssens E, Timmerman V, Guns PJ, De Meyer GRY, Martinet W. Partial Inhibition of Glycolysis Reduces Atherogenesis Independent of Intraplaque Neovascularization in Mice. *Arterioscler Thromb Vasc Biol* 2020; **40**: 1168-1181 [PMID: 32188275 DOI: 10.1161/atvbaha.119.313692]

21 **An Q**, Li C, Chen Y, Yang Y, Song R, Zhou L, Li J, Tong A, Luo Y. Scaffold hopping of agomelatine leads to enhanced antidepressant effects by modulation of gut microbiota and host immune responses. *Pharmacol Biochem Behav* 2020; **192**: 172910 [PMID: 32194087 DOI: 10.1016/j.pbb.2020.172910]

22 **Figueiredo AA**, Sales TMAL, Nicolau LAD, Nunes AAA, Costa-Filho HB, Moreira RLR, Nascimento RR, Sousa MKA, Silva LD, Carmo-Neto JP, Sidou FMNO, Paula SM, Medeiros JVR, Silva DA, Sifrim D, Souza MHLP. Laryngeal Mucosa Alterations in Mice Model of Gastroesophageal Reflux: Effects of Topical Protection. *Laryngoscope* 2020 [PMID: 32159864 DOI: 10.1002/Lary.28597]

23 **Dong C**, Wu G, Li H, Qiao Y, Gao S. Ampelopsin inhibits high glucose-induced extracellular matrix accumulation and oxidative stress in mesangial cells through activating the Nrf2/HO-1 pathway. *Phytother Res* 2020 [PMID: 32155298 DOI: 10.1002/ptr.6668]

24 **Shao Q**, Xue S, Jiang Y, Lu H, Sang W, Wang C, Xue B, Liu Y, Zhu L, Ma J. Esculentoside A protects against osteoarthritis by ameliorating inflammation and repressing osteoclastogenesis. *Int Immunopharmacol* 2020; **82**: 106376 [PMID: 32163857 DOI: 10.1016/j.intimp.2020.106376]

25 **Li W**, Zhang X, Chen R, Li Y, Miao J, Liu G, Lan Y, Chen Y, Cao Y. HPLC fingerprint analysis of Phyllanthus emblica ethanol extract and their antioxidant and anti-inflammatory properties. *J Ethnopharmacol* 2020; **254**: 112740 [PMID: 32151757 DOI: 10.1016/j.jep.2020.112740]

26 **Wang L**, Chen Q, Zhuang S, Wen Y, Cheng W, Zeng Z, Jiang T, Tang C. Effect of Anoectochilus roxburghii flavonoids extract on H2O2 - Induced oxidative stress in LO2 cells and D-gal induced aging mice model. *J Ethnopharmacol* 2020; **254**: 112670 [PMID: 32135242 DOI: 10.1016/j.jep.2020.112670]

27 **Jarosz-Griffiths HH**, Scambler T, Wong CH, Lara-Reyna S, Holbrook J, Martinon F, Savic S, Whitaker P, Etherington C, Spoletini G, Clifton I, Mehta A, McDermott MF, Peckham D. Different CFTR modulator combinations downregulate inflammation differently in cystic fibrosis. *Elife* 2020; **9**: [PMID: 32118580 DOI: 10.7554/eLife.54556]

28 **Liu Z**, Jiao Y, Lu H, Shu X, Chen Q. Chemical characterization, antioxidant properties and anticancer activity of exopolysaccharides from Floccularia luteovirens. *Carbohydr Polym* 2020; **229**: 115432 [PMID: 31826528 DOI: 10.1016/j.carbpol.2019.115432]

29 **Wang L**, Kim HS, Oh JY, Je JG, Jeon YJ, Ryu B. Protective effect of diphlorethohydroxycarmalol isolated from Ishige okamurae against UVB-induced damage *in vitro* in human dermal fibroblasts and *in vivo* in zebrafish. *Food Chem Toxicol* 2020; **136**: 110963 [PMID: 31715308 DOI: 10.1016/j.fct.2019.110963]

30 **Hasan R**, Lindarto D, Siregar GA, Mukhtar Z. The effect of bay leaf extract Syzygium polyanthum (Wight) Walp. on C-reactive protein (CRP) and myeloperoxidase (MPO) level in the heart of rat model of myocardial infarction. *Med Glas (Zenica)* 2020; **17**: [PMID: 31601063 DOI: 10.17392/1068-20]

31 **Kabel AM**, Estfanous RS, Alrobaian MM. Targeting oxidative stress, proinflammatory cytokines, apoptosis and toll like receptor 4 by empagliflozin to ameliorate bleomycin-induced lung fibrosis. *Respir Physiol Neurobiol* 2020; **273**: 103316 [PMID: 31600583 DOI: 10.1016/j.resp.2019.103316]

32 **Zhang Y**, Cui Y, Dai S, Deng W, Wang H, Qin W, Yang H, Liu H, Yue J, Wu D, Wang J, Guo H. Isorhynchophylline enhances Nrf2 and inhibits MAPK pathway in cardiac hypertrophy. *Naunyn Schmiedebergs Arch Pharmacol* 2020; **393**: 203-212 [PMID: 31489470 DOI: 10.1007/s00210-019-01716-0]

33 **Yang JH**, Na CS, Cho SS, Kim KM, Lee JH, Chen XQ, Ku SK, Cho IJ, Kim EJ, Lee JH, Ki SH. Hepatoprotective Effect of Neoagarooligosaccharide via Activation of Nrf2 and Enhanced Antioxidant Efficacy. *Biol Pharm Bull* 2020; **43**: 619-628 [PMID: 32009027 DOI: 10.1248/bpb.b19-00697]

34 **Nguyen S**, Castellanos KA, Abraham A, Ferrini MG. Reduction of oxidative stress markers in the corpora cavernosa and media of penile dorsal artery in middle-aged rats treated with COMP-4. *Int J Impot Res* 2020 [PMID: 32005937 DOI: 10.1038/s41443-020-0233-9]

35 **Li L**, Chen J, Lin L, Pan G, Zhang S, Chen H, Zhang M, Xuan Y, Wang Y, You Z. Quzhou Fructus Aurantii Extract suppresses inflammation via regulation of MAPK, NF-κB, and AMPK signaling pathway. *Sci Rep* 2020; **10**: 1593 [PMID: 32005962 DOI: 10.1038/s41598-020-58566-7]

36 **Alam MB**, Chowdhury NS, Sohrab MH, Rana MS, Hasan CM, Lee SH. Cerevisterol Alleviates Inflammation via Suppression of MAPK/NF-κB/AP-1 and Activation of the Nrf2/HO-1 Signaling Cascade. *Biomolecules* 2020; **10**: [PMID: 32013140 DOI: 10.3390/biom10020199]

37 **Lee W**, Kim J, Park EK, Bae JS. Maslinic Acid Ameliorates Inflammation via the Downregulation of NF-κB and STAT-1. *Antioxidants (Basel)* 2020; **9**: [PMID: 31991739 DOI: 10.3390/antiox9020106]

38 **Jung TY**, Lee AY, Song JH, Lee MY, Lim JO, Lee SJ, Ko JW, Shin NR, Kim JC, Shin IS, Kim JS. *Scrophularia koraiensis* Nakai Attenuates Allergic Airway Inflammation via Suppression of NF-κB and Enhancement of Nrf2/HO-1 Signaling. *Antioxidants (Basel)* 2020; **9**: [PMID: 31991647 DOI: 10.3390/antiox9020099]

39 **Seedevi P**, Ramu Ganesan A, Moovendhan M, Mohan K, Sivasankar P, Loganathan S, Vairamani S, Shanmugam A. Anti-diabetic activity of crude polysaccharide and rhamnose-enriched polysaccharide from G. lithophila on Streptozotocin (STZ)-induced in Wistar rats. *Sci Rep* 2020; **10**: 556 [PMID: 31953455 DOI: 10.1038/s41598-020-57486-w]

40 **Wang S**, Xu J, Zheng J, Zhang X, Shao J, Zhao L, Hao J. Anti-Inflammatory and Antioxidant Effects of Acetyl-L-Carnitine on Atherosclerotic Rats. *Med Sci Monit* 2020; **26**: e920250 [PMID: 31945029 DOI: 10.12659/msm.920250]

41 **Gawish RA**, Fahmy HA, Abd El Fattah AI, Nada AS. The potential effect of methylseleninic acid (MSA) against γ-irradiation induced testicular damage in rats: Impact on JAK/STAT pathway. *Arch Biochem Biophys* 2020; **679**: 108205 [PMID: 31758927 DOI: 10.1016/j.abb.2019.108205]

42 **Wang J**, Gao Y, Lin F, Han K, Wang X. Omentin-1 attenuates lipopolysaccharide (LPS)-induced U937 macrophages activation by inhibiting the TLR4/MyD88/NF-κB signaling. *Arch Biochem Biophys* 2020; **679**: 108187 [PMID: 31706880 DOI: 10.1016/j.abb.2019.108187]

43 **Kim SM**, Vetrivel P, Kim HH, Ha SE, Saralamma VVG, Kim GS. *Artemisia iwayomogi* (Dowijigi) inhibits lipopolysaccharide-induced inflammation in RAW264.7 macrophages by suppressing the NF-κB signaling pathway. *Exp Ther Med* 2020; **19**: 2161-2170 [PMID: 32104280 DOI: 10.3892/etm.2020.8472]

44 **Kim HJ**, Joe HI, Zhang Z, Woo Lee S, Lee KY, Kook YB, An HJ. Anti-inflammatory effect of Acalypha australis L. via suppression of NF-κB signaling in LPS-stimulated RAW 264.7 macrophages and LPS-induced septic mice. *Mol Immunol* 2020; **119**: 123-131 [PMID: 32014631 DOI: 10.1016/j.molimm.2020.01.010]

45 **Yang X**, Wei HM, Hu GY, Zhao J, Long LN, Li CJ, Zhao ZJ, Zeng HK, Nie H. Combining antioxidant astaxantin and cholinesterase inhibitor huperzine A boosts neuroprotection. *Mol Med Rep* 2020; **21**: 1043-1050 [PMID: 31922239 DOI: 10.3892/mmr.2020.10920]

46 **Khan AM**, Khan AU, Ali H, Islam SU, Seo EK, Khan S. Continentalic acid exhibited nephroprotective activity against the LPS and E. coli-induced kidney injury through inhibition of the oxidative stress and inflammation. *Int Immunopharmacol* 2020; **80**: 106209 [PMID: 32004924 DOI: 10.1016/j.intimp.2020.106209]

47 **Qu Z**, Chen Y, Luo ZH, Shen XL, Hu YJ. 7-methoxyflavanone alleviates neuroinflammation in lipopolysaccharide-stimulated microglial cells by inhibiting TLR4/MyD88/MAPK signalling and activating the Nrf2/NQO-1 pathway. *J Pharm Pharmacol* 2020; **72**: 385-395 [PMID: 31867739 DOI: 10.1111/jphp.13219]

48 **Ohno O**, Terasaki T, Sano T, Hitomi Y, Miyamoto J, Matsuno K. Inhibitory effects of biseokeaniamide A against lipopolysaccharide-induced signal transduction. *Bioorg Med Chem Lett* 2020; **30**: 127069 [PMID: 32173199 DOI: 10.1016/j.bmcl.2020.127069]

49 **Kurt B**, Ozleyen A, Antika G, Yilmaz YB, Tumer TB. Multitarget Profiling of a Strigolactone Analogue for Early Events of Alzheimer's Disease: In Vitro Therapeutic Activities against Neuroinflammation. *ACS Chem Neurosci* 2020; **11**: 501-507 [PMID: 32017526 DOI: 10.1021/acschemneuro.9b00694]

50 **Shi K**, Zhu J, Chen D, Ren C, Guo M, Wang J, Wu X, Feng Y. Lipidomics Analysis of Timosaponin BII in INS-1 Cells Induced by Glycolipid Toxicity and Its Relationship with Inflammation. *Chem Biodivers* 2020; **17**: e1900684 [PMID: 32064755 DOI: 10.1002/cbdv.201900684]

51 **Ren YS**, Li HH, Yao JC, Tan YJ, Pan LH, Peng T, Zhao LL, Zhang GM, Yue J, Hu XM, Liu Z, Li J. Application quantitative proteomics approach to identify differentially expressed proteins associated with cardiac protection mediated by cycloastragenol in acute myocardial infarction rats. *J Proteomics* 2020; **222**: 103691 [PMID: 32068187 DOI: 10.1016/j.jprot.2020.103691]

52 **Sousa NA**, Oliveira GAL, de Oliveira AP, Lopes ALF, Iles B, Nogueira KM, Araújo TSL, Souza LKM, Araújo AR, Ramos-Jesus J, Plácido A, Amaral C, Campelo YDM, Barbosa EA, Portugal CC, Socodato R, Lobo A, Relvas J, Bemquerer M, Eaton P, Leite JRSA, Medeiros JVR. Novel Ocellatin Peptides Mitigate LPS-induced ROS Formation and NF-kB Activation in Microglia and Hippocampal Neurons. *Sci Rep* 2020; **10**: 2696 [PMID: 32060388 DOI: 10.1038/s41598-020-59665-1]

53 **Linghu KG**, Ma QS, Zhao GD, Xiong W, Lin L, Zhang QW, Bian Z, Wang Y, Yu H. Leocarpinolide B attenuates LPS-induced inflammation on RAW264.7 macrophages by mediating NF-κB and Nrf2 pathways. *Eur J Pharmacol* 2020; **868**: 172854 [PMID: 31837308 DOI: 10.1016/j.ejphar.2019.172854]

54 **Ma WQ**, Cheng HZ, Zhao DH, Yang J, Wang SB, Wu HZ, Lu MY, Xu L, Liu GJ. Effects of dietary Enteromorpha powder supplementation on productive performance, egg quality, and antioxidant performance during the late laying period in Zi geese. *Poult Sci* 2020; **99**: 1062-1068 [PMID: 32029142 DOI: 10.1016/j.psj.2019.10.003]

55 **Zhao P**, Zhou W, Zhang Y, Li J, Zhao Y, Pan L, Shen Z, Chen W, Hui J. Aminooxyacetic acid attenuates post-infarct cardiac dysfunction by balancing macrophage polarization through modulating macrophage metabolism in mice. *J Cell Mol Med* 2020; **24**: 2593-2609 [PMID: 31930778 DOI: 10.1111/jcmm.14972]

56 **Liu XC**, Wu CZ, Hu XF, Wang TL, Jin XP, Ke SF, Wang E, Wu G. Gastrodin Attenuates Neuronal Apoptosis and Neurological Deficits after Experimental Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis* 2020; **29**: 104483 [PMID: 31727597 DOI: 10.1016/j.jstrokecerebrovasdis.2019.104483]

57 **Shi C**, Zhang H, Wang X, Jin B, Jia Q, Li Y, Yang Y. Cinnamtannin D1 attenuates autoimmune arthritis by regulating the balance of Th17 and treg cells through inhibition of aryl hydrocarbon receptor expression. *Pharmacol Res* 2020; **151**: 104513 [PMID: 31706010 DOI: 10.1016/j.phrs.2019.104513]

58 **Zhang C**, Zhao X, Lin S, Liu F, Ma J, Han Z, Jia F, Xie W, Zhang Q, Li X. Neuroprotective Effect of *ent*-Kaur-15-en-17-al-18-oic Acid on Amyloid Beta Peptide-Induced Oxidative Apoptosis in Alzheimer's Disease. *Molecules* 2019; **25**: [PMID: 31905798 DOI: 10.3390/molecules25010142]

59 **Akhtar M**, Shaukat A, Zahoor A, Chen Y, Wang Y, Yang M, Umar T, Guo M, Deng G. Hederacoside-C Inhibition of Staphylococcus aureus-Induced Mastitis via TLR2 & TLR4 and Their Downstream Signaling NF-κB and MAPKs Pathways In Vivo and In Vitro. *Inflammation* 2020; **43**: 579-594 [PMID: 31845052 DOI: 10.1007/s10753-019-01139-2]

60 **Cernackova A**, Mikova L, Horvathova L, Tillinger A, Mravec B. Cachexia induced by Yoshida ascites hepatoma in Wistar rats is not associated with inflammatory response in the spleen or brain. *J Neuroimmunol* 2019; **337**: 577068 [PMID: 31606594 DOI: 10.1016/j.jneuroim.2019.577068]

61 **Yeo HJ**, Shin MJ, You JH, Kim JS, Kim MY, Kim DW, Kim DS, Eum WS, Choi SY. Transduced Tat-CIAPIN1 reduces the inflammatory response on LPS- and TPA-induced damages. *BMB Rep* 2019; **52**: 695-699 [PMID: 31722779]

62 **Ercan G**, Ä°lbar Tartar R, Solmaz A, Gulcicek OB, Karagulle OO, Meric S, Cayoren H, Kusaslan R, Kemik A, Gokceoglu Kayali D, Cetinel S, Celik A. Examination of protective and therapeutic effects of ruscogenin on cerulein-induced experimental acute pancreatitis in rats. *Ann Surg Treat Res* 2019; **97**: 271-281 [PMID: 31824881 DOI: 10.4174/astr.2019.97.6.271]

63 **Yang Z**, Pan Y, Chen J, Zhang H, Wei H, Wu Z, Liu L. Anti-inflammatory, anti-oxidative stress effect of *Phascolosoma esculenta* oligosaccharides on *Escherichia coli*-induced sepsis mice. *Food Sci Biotechnol* 2019; **28**: 1871-1879 [PMID: 31807361 DOI: 10.1007/s10068-019-00620-w]

64 **Narimiya T**, Kanzaki H, Yamaguchi Y, Wada S, Katsumata Y, Tanaka K, Tomonari H. Nrf2 activation in osteoblasts suppresses osteoclastogenesis via inhibiting IL-6 expression. *Bone Rep* 2019; **11**: 100228 [PMID: 31763378 DOI: 10.1016/j.bonr.2019.100228]

65 **Shi X**, Pan S, Li Y, Ma W, Wang H, Xu C, Li L. Xanthoplanine attenuates macrophage polarization towards M1 and inflammation response via disruption of CrkL-STAT5 complex. *Arch Biochem Biophys* 2020; **683**: 108325 [PMID: 32142888 DOI: 10.1016/j.abb.2020.108325]

66 **Li P**, Liu Q, Zhang T, Guo W, Qiao W, Deng M. Protective Effects of Lixisenatide against Lipopolysaccharide-Induced Inflammation Response in MAC-T Bovine Mammary Epithelial Cells: A Therapeutic Implication in Mastitis. *Chem Res Toxicol* 2020; **33**: 982-987 [PMID: 32191445 DOI: 10.1021/acs.chemrestox.9b00524]

67 **Wang YS**, Teng GQ, Zhou H, Dong CL. Germanium Reduces Inflammatory Damage in Mammary Glands During Lipopolysaccharide-Induced Mastitis in Mice. *Biol Trace Elem Res* 2020 [PMID: 32144718 DOI: 10.1007/s12011-020-02106-x]

68 **Garcia-Just A**, Miró L, Pérez-Bosque A, Amat C, Polo J, Pallàs M, Griñán-Ferré C, Moretó M. Dietary Spray-Dried Porcine Plasma Prevents Cognitive Decline in Senescent Mice and Reduces Neuroinflammation and Oxidative Stress. *J Nutr* 2020; **150**: 303-311 [PMID: 31562503 DOI: 10.1093/jn/nxz239]

69 **Chen C**, You F, Wu F, Luo Y, Zheng G, Xu H, Liu Y. Antiangiogenesis Efficacy of Ethanol Extract from *Amomum tsaoko* in Ovarian Cancer through Inducing ER Stress to Suppress p-STAT3/NF-kB/IL-6 and VEGF Loop. *Evid Based Complement Alternat Med* 2020; **2020**: 2390125 [PMID: 32190078 DOI: 10.1155/2020/2390125]

70 **Logozzi M**, Mizzoni D, Di Raimo R, Andreotti M, Macchia D, Spada M, Fais S. *In vivo* antiaging effects of alkaline water supplementation. *J Enzyme Inhib Med Chem* 2020; **35**: 657-664 [PMID: 32106720 DOI: 10.1080/14756366.2020.1733547]

71 **Yang L**, Tong Y, Chen PF, Miao S, Zhou RY. Neuroprotection of dihydrotestosterone via suppression of the toll-like receptor 4/nuclear factor-kappa B signaling pathway in high glucose-induced BV-2 microglia inflammatory responses. *Neuroreport* 2020; **31**: 139-147 [PMID: 31876682 DOI: 10.1097/wnr.0000000000001385]

72 **Zhou H**, Zhu ZH, Liu Y, Liu YY. Effects of midazolam combined with sufentanil on injury and expression of HMGB1 and NF-κB in rats with pancreatitis. *Eur Rev Med Pharmacol Sci* 2020; **24**: 2102-2109 [PMID: 32141580 DOI: 10.26355/eurrev\_202002\_20390]

73 **Zhang C**, Jiang M, Wang WQ, Zhao SJ, Yin YX, Mi QJ, Yang MF, Song YQ, Sun BL, Zhang ZY. Selective mGluR1 Negative Allosteric Modulator Reduces Blood-Brain Barrier Permeability and Cerebral Edema After Experimental Subarachnoid Hemorrhage. *Transl Stroke Res* 2020; **11**: 799-811 [PMID: 31833035 DOI: 10.1007/s12975-019-00758-z]

74 **Che L**, Li Y, Song R, Qin C, Hao W, Wang B, Yang L, Peng P, Xu F. Anti-inflammatory and anti-apoptosis activity of taraxasterol in ulcerative colitis *in vitro* and *in vivo*. *Exp Ther Med* 2019; **18**: 1745-1751 [PMID: 31410133 DOI: 10.3892/etm.2019.7736]

75 **Piao T**, Ma Z, Li X, Liu J. Taraxasterol inhibits IL-1β-induced inflammatory response in human osteoarthritic chondrocytes. *Eur J Pharmacol* 2015; **756**: 38-42 [PMID: 25797286 DOI: 10.1016/j.ejphar.2015.03.012]

76 **Liu J**, Cai J, Fan P, Zhang N, Cao Y. The Abilities of Salidroside on Ameliorating Inflammation, Skewing the Imbalanced Nucleotide Oligomerization Domain-Like Receptor Family Pyrin Domain Containing 3/Autophagy, and Maintaining Intestinal Barrier Are Profitable in Colitis. *Front Pharmacol* 2019; **10**: 1385 [PMID: 31849652 DOI: 10.3389/fphar.2019.01385]

77 **Li H**, Shen L, Lv T, Wang R, Zhang N, Peng H, Diao W. Salidroside attenuates dextran sulfate sodium-induced colitis in mice via SIRT1/FoxOs signaling pathway. *Eur J Pharmacol* 2019; **861**: 172591 [PMID: 31401159 DOI: 10.1016/j.ejphar.2019.172591]

78 **Wang J**, Pan Y, Cao Y, Zhou W, Lu J. Salidroside regulates the expressions of IL-6 and defensins in LPS-activated intestinal epithelial cells through NF-κB/MAPK and STAT3 pathways. *Iran J Basic Med Sci* 2019; **22**: 31-37 [PMID: 30944705 DOI: 10.22038/ijbms.2018.26994.6602]

79 **Kim SH**, Hyun SH, Choung SY. Antioxidative effects of Cinnamomi cassiae and Rhodiola rosea extracts in liver of diabetic mice. *Biofactors* 2006; **26**: 209-219 [PMID: 16971752 DOI: 10.1002/biof.5520260306]

80 **Yu T**, Wan P, Zhu XD, Ren YP, Wang C, Yan RW, Guo Y, Bai AP. Inhibition of NADPH oxidase activities ameliorates DSS-induced colitis. *Biochem Pharmacol* 2018; **158**: 126-133 [PMID: 30321511 DOI: 10.1016/j.bcp.2018.10.010]

81 **Frasier CR**, Moukdar F, Patel HD, Sloan RC, Stewart LM, Alleman RJ, La Favor JD, Brown DA. Redox-dependent increases in glutathione reductase and exercise preconditioning: role of NADPH oxidase and mitochondria. *Cardiovasc Res* 2013; **98**: 47-55 [PMID: 23341578 DOI: 10.1093/cvr/cvt009]

82 **Lin Y**, Zheng X, Chen J, Luo D, Xie J, Su Z, Huang X, Yi X, Wei L, Cai J, Sun Z. Protective Effect of *Bruguiera gymnorrhiza* (L.) Lam. Fruit on Dextran Sulfate Sodium-Induced Ulcerative Colitis in Mice: Role of Keap1/Nrf2 Pathway and Gut Microbiota. *Front Pharmacol* 2019; **10**: 1602 [PMID: 32116661 DOI: 10.3389/fphar.2019.01602]

83 **Zhou Y**, Park CM, Cho CW, Song YS. Protective effect of pinitol against D-galactosamine-induced hepatotoxicity in rats fed on a high-fat diet. *Biosci Biotechnol Biochem* 2008; **72**: 1657-1666 [PMID: 18603811 DOI: 10.1271/bbb.70473]

84 **Gao XJ**, Li T, Wei B, Yan ZX, Yan R. [Regulatory mechanisms of gut microbiota on intestinal CYP3A and P-glycoprotein in rats with dextran sulfate sodium-induced colitis]. *Yao Xue Xue Bao* 2017; **52**: 34-43 [PMID: 29911375]

85 **Rice TW**, Wheeler AP, Bernard GR, Vincent JL, Angus DC, Aikawa N, Demeyer I, Sainati S, Amlot N, Cao C, Ii M, Matsuda H, Mouri K, Cohen J. A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Crit Care Med* 2010; **38**: 1685-1694 [PMID: 20562702 DOI: 10.1097/CCM.0b013e3181e7c5c9]

86 **Corsale I**, Carrieri P, Martellucci J, Piccolomini A, Verre L, Rigutini M, Panicucci S. Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of I-III degree hemorroidal disease: a double-blind multicenter prospective comparative study. *Int J Colorectal Dis* 2018; **33**: 1595-1600 [PMID: 29934701 DOI: 10.1007/s00384-018-3102-y]

87 **Fan SH**, Zhang ZF, Zheng YL, Lu J, Wu DM, Shan Q, Hu B, Wang YY. Troxerutin protects the mouse kidney from d-galactose-caused injury through anti-inflammation and anti-oxidation. *Int Immunopharmacol* 2009; **9**: 91-96 [PMID: 19000936 DOI: 10.1016/j.intimp.2008.10.008]

88 **Colombo BB**, Fattori V, Guazelli CFS, Zaninelli TH, Carvalho TT, Ferraz CR, Bussmann AJC, Ruiz-Miyazawa KW, Baracat MM, Casagrande R, Verri WA Jr. Vinpocetine Ameliorates Acetic Acid-Induced Colitis by Inhibiting NF-κB Activation in Mice. *Inflammation* 2018; **41**: 1276-1289 [PMID: 29633103 DOI: 10.1007/s10753-018-0776-9]

89 **Imamoto T**, Tanabe M, Shimamoto N, Kawazoe K, Hirata M. Cerebral circulatory and cardiac effects of vinpocetine and its metabolite, apovincaminic acid, in anesthetized dogs. *Arzneimittelforschung* 1984; **34**: 161-169 [PMID: 6539108]

90 **Liu X**, Yu X, Xu X, Zhang X, Zhang X. The protective effects of Poria cocos-derived polysaccharide CMP33 against IBD in mice and its molecular mechanism. *Food Funct* 2018; **9**: 5936-5949 [PMID: 30378628 DOI: 10.1039/c8fo01604f]

91 **Wang Q**, Chen S, Han L, Lian M, Wen Z, Jiayinaguli T, Liu L, Sun R, Cao Y. Antioxidant activity of carboxymethyl (1→3)-β-d-glucan (from the sclerotium of Poria cocos) sulfate (in vitro). *Int J Biol Macromol* 2014; **69**: 229-235 [PMID: 24875321 DOI: 10.1016/j.ijbiomac.2014.05.038]

92 **Nowotarska SW**, Nowotarski K, Grant IR, Elliott CT, Friedman M, Situ C. Mechanisms of Antimicrobial Action of Cinnamon and Oregano Oils, Cinnamaldehyde, Carvacrol, 2,5-Dihydroxybenzaldehyde, and 2-Hydroxy-5-Methoxybenzaldehyde against Mycobacterium avium subsp. paratuberculosis (Map). *Foods* 2017; **6**: [PMID: 28837070 DOI: 10.3390/foods6090072]

93 **Jayakumar S**, Madankumar A, Asokkumar S, Raghunandhakumar S, Gokula dhas K, Kamaraj S, Divya MG, Devaki T. Potential preventive effect of carvacrol against diethylnitrosamine-induced hepatocellular carcinoma in rats. *Mol Cell Biochem* 2012; **360**: 51-60 [PMID: 21879312 DOI: 10.1007/s11010-011-1043-7]

94 **Xiao J**, Wang J, Chen Y, Zhou Z, Gao C, Guo Z. Sauchinone ameliorates intestinal inflammation and promotes Th17 cell production of IL-10 via Blimp-1. *Biochem Biophys Res Commun* 2020; **522**: 435-441 [PMID: 31771884 DOI: 10.1016/j.bbrc.2019.11.122]

95 **Lee WS**, Baek YI, Kim JR, Cho KH, Sok DE, Jeong TS. Antioxidant activities of a new lignan and a neolignan from Saururus chinensis. *Bioorg Med Chem Lett* 2004; **14**: 5623-5628 [PMID: 15482936 DOI: 10.1016/j.bmcl.2004.08.054]

**Footnotes**

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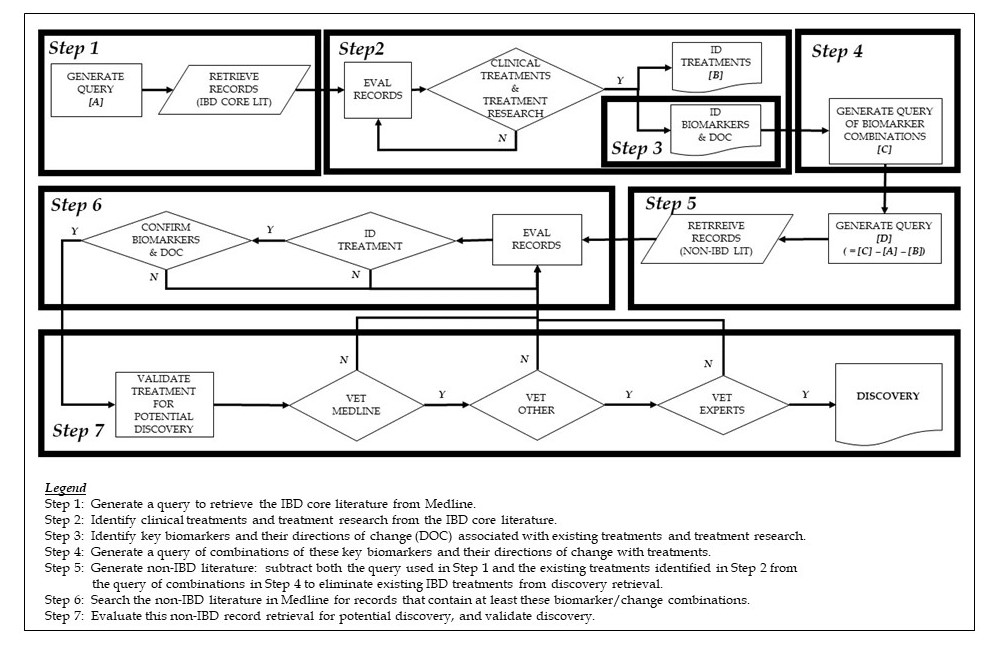
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**Figure Legends**



**Figure 1 literature-related discovery and innovation treatment repurposing flow diagram.**

**Table 1 Potential novel treatments**

|  |  |  |
| --- | --- | --- |
| **Treatment** | **Biomarkers changed in desired direction** | **Ref.** |
| Fluprostenol | iNOS, TNF-α, CD11c, IL-10, NF-kB, p65 | [10] |
| Liu Shen Wan | Anti-inflammatory, IL-1β, TNF-α, IFN-γ, IL-6, TLR4, NF-kB p65, p-IkBα | [11] |
| Erdosteine | Anti-oxidant, anti-inflammatory, IL-1β, COX-2, iNOS, P65,  ADAMTS-5, MMP1, MMP3, MMP-13, MAPK, Wnt/β-catenin | [12] |
| 4-Octyl itaconate | Anti-inflammatory, TGF-β/Smad, NF-kB, ROS, autophagy | [13] |
| 2 ,3-dihydro-5,6-dimethoxy-1H-inden-1-one | ROS, LDH, MDA, TAC, anti-inflammatory | [14] |
| Neutrophilic granule protein | TNF-α, IL-1β, NF-kB, IL-10, anti-inflammatory | [15] |
| Dioscorea zingiberensis | BTB integrity, ZO-1, MDA, 8-OHdG, Nrf2, NOQ1, HO-1 | [16] |
| FCPR16 | TNF-α, Caspase-3, Caspase-8, NF-kB p65, iNOS, ROS, JNK | [17] |
| 7,8-dihydroxyflavone | GSH, nitrite, MDA, NF-kB, iNOS, caspase-3, Nrf2, HO-1, BDNF | [18] |
| X-inactive specific transcript | Anti-inflammatory, NF-kB, IL-6 | [19] |
| 3-[3-pyridinyl]-1-[4-pyridinyl]-2-propen-1-one | M1, autophagy, NF-kB, TNF-α, ICAM-1, VCAM-1 | [20] |
| NMDEA | IL-1β, IL-6, p65, iNOS | [21] |
| Cashew gum | MPO, TER, anti-inflammatory, barrier function | [22] |
| Ampelopsin | ROS, NOX2, NOX4, FN, Col IV, Nrf2, HO-1, NQO-1 | [23] |
| Esculentoside A | IL-1β, IL-6, IL-8, TNF-α, MMP -2, -3, -13, NF-kB, MAPK | [24] |
| Phyllanthus emblica | Antioxidant, GSH, SOD, MDA, inflammation | [25] |
| Anoectochilus roxburghii | Oxidative stress, SOD, GSH-PX, MDA, GPx-1, GPx-4 | [26] |
| Ivacaftor; Tezacaftor | IL-18, IL-1β, TNF, Caspase-1, IL-10, Anti-inflammatory | [27] |
| Floccularia luteovirens | SOD, GSH-Px, CAT, MDA, ROS, oxidative stress | [28] |
| Ishige okamurae; DPHC | ROS, elastase, MMPs, NF-kB, AP-1, MAPKs | [29] |
| Syzygium polyanthum (Wight) walp.; Bay leaf | CRP, MPO, anti-inflammatory | [30] |
| Empagliflozin | LDH, total leucocytic count, IL-6, TNF-α, TLR4, TGF-β1, oxidative stress, Nrf2/HO-1 | [31] |
| Isorhynchophylline | Antioxidant, TGF-β1, CTGF, 4-HNE, MDA, Nrf2, MAPK | [32] |
| Neoagarooligosaccharide | Nrf2, GSH, glutathione, ROS, inflammation, antioxidant | [33] |
| COMP-4; Muira puama | NO, antioxidative, apoptosis, HO-1, MPO, GSH/GSSG ratio | [34] |
| Quzhou fructus aurantii | Anti-inflammatory, MAPK, NF-kB, TNF, IL-6, IL-1β, IL-10 | [35] |
| Cerevisterol | MAPK, NF-kB, AP-1, Nrf2, HO-1, anti-inflammatory | [36] |
| Maslinic acid | HO-1, COX-2/PGE2, STAT-1, Nrf2, IL-1, iNOS, NF-kB | [37] |
| Scrophularia koraiensis nakai; Scrophulariaceae | Ig-E, anti-inflammatory, NF-kB, Nrf-2, HO-1 | [38] |
| Grateloupia lithophila | Blood glucose, TC, TGs, LDL, VLDL, HDL, SOD, GPx, MDA | [39] |
| Acetyl-l-carnitine | LDL, HDL, SOD, GSH-Px MDA, TNF-α, IL-1SS, iNOS, CRP | [40] |
| Methylseleninic acid | GPx, Nrf2, Socs3, p-JAK1, p-STAT3, NF-kB | [41] |
| Omentin-1 | Pro-inflammatory cytokines, NF-kB, Nrf2 | [42] |
| Dowijigi | NO, PGE2, TNF-α, IL-6, IL-1β, COX2, iNOS, NF-kB | [43] |
| AAL | NO, iNOS, TNF-α, IL-6, IL-1β, NF-kB | [44] |
| AXT and HupA | Oxidative stress, LDH, ROS, SOD, MDA | [45] |
| Continentalic acid (CNT) | GSH, GST, catalase, SOD, MDA, POD, MPO, NO, Nrf2, iNOS | [46] |
| 7-Methoxyflavanone (7MF) | IL-6, TNF-α, COX-2, iNOS, ICAM-1, MCP-1, TLR4, MyD88, p-JNK, p-ERK, Nrf2, NQO-1, Iba1 | [47] |
| Biseokeaniamide A | NO, iNOS, IL-1β, IkBα | [48] |
| Strigolactone GR24 | NF-kB, Nrf2, PPARγ, occludin | [49] |
| Timosaponin BII | MDA, GSH, PS, NLRP3, IL-1β, oxidative stress | [50] |
| Cycloastragenol (Y006) | BAX, COX2, GSK3β, TNF-α, IFN-γ, IL-17, IL-10, IL-4 | [51] |
| Ocellatin-K1(1-16); Ocellatin-K1(1-21) | Nitrite, MDA, SOD, GSH, ROS, NF-kB, oxidative stress | [52] |
| Leocarpinolide B (LB) | NO, PGE2, IL-6, TNF-α, MCP-1, COX-2, iNOS, NF-kB, ROS, HO-1, Nrf2 | [53] |
| Enteromorpha powder | GSH-Px, MDA, lipid peroxidation | [54] |
| Aminooxyacetic acid (AOAA) | ATP, IL-6, TNF-α, IL-10, NLRP3, caspase-1, IL-1β | [55] |
| Gastrodin | ROS, 8-OHDG, MDA, GSH-Px, SOD, Nrf2, HO-1, Bcl-2, Bax, caspase-3 | [56] |
| Cinnamtannin D1 (CTD-1) | IL-17, IL-6, IL-1β, TGF-β, IL-10, Th17, Treg, STAT5/Foxp3 | [57] |
| ent-Kaur-15-en-17-al-18-oic acid | ROS, MDA, GSH, SOD, NF-kB, bcl-2, p53, Bax, caspase-3 | [58] |
| Hederacoside-C (HDC) | IL-6, IL-1β, TNF-α, IL-10, TLR2, TLR4, MAPKs, NF-kB | [59] |
| PS-1145 dihydrochloride | IL-6, TNF-α, IL-1β, NF-kB, COX-2 | [60] |
| Cytokine-induced apoptosis inhibitor 1 (CIAPIN1) | ROS, MAPKs, NF-kB, Bax, caspase-3, COX-2, iNOS, IL-6, TNF-α | [61] |
| Ruscogenin | CRP, TNF-α, IL-6, IL-1β, ICAM-1, NF-kB, NOS-1 | [62] |
| Phascolosoma esculenta | IL-1β, TNF-α, IL-10, MDA, Nrf2, inflammation, oxidation | [63] |
| ALA/SFC | Anti-oxidation, RANKL, IL-6, Nrf2 | [64] |
| Xanthoplanine | Inflammatory cytokines, ROS, STAT5 | [65] |
| Lixisenatide | ROS, NADPH, NOX-1, TNF-α, IL-6, IL-1β, MMP -2 -9, TLR4, NF-kB | [66] |
| Germanium | MPO, TNF-α, IL-1β, IL-6, IL-10, NF-kB p65, p38, ERK, JNK | [67] |
| SDP | Permeability, ZO-1, E-cadherin, NFkB, Il-6, hydrogen peroxide, IL-10 | [68] |
| Amomum tsaoko | IL-6, VEGF, Nh-kB, P-STAT3 | [69] |
| Alkaline water | ROS, SOD-1, GSH, telomerase activity, telomeres length | [70] |
| Dihydrotestosterone | NO, PGE2, iNOS, COX-2, TNF-α, IL-1β, TLR4, NF-kB | [71] |
| Midazolam/Sufentanil | TNF-α, IL-1β, HMGB1, NF-kB, ROS, SOD, inflammatory | [72] |
| JNJ16259685 | Permeability, VASP, p-VASP, occludin, AQP | [73] |

**Table 2 Recently identified potential inflammatory bowel disease treatments.**

|  |  |  |
| --- | --- | --- |
| **Treatment** | **Biomarkers changed in desired direction** | **Ref.** |
| Taraxasterol | ROS, MDA, Caspase-3, Bcl-2, Bax, Nrf2, HO-1, NQO-1, GPx-3 | [74,75] |
| Rhodiola rosea; Salidroside | IL-6, sIL-6R, IFN-γ, IL-17A, IL-4, Th1 cells, Th17 cells, Treg cells, JAK1, JAK2, STAT3, RORγt | [76-79] |
| VAS2870 | Nox2, ROS, epithelium barrier integrity, cell viability | [80,81] |
| Pinitol | Oxidative stress, ROS, TNF-α, IL-1β, IL-6, NO, PGE2, iNOS, COX-2, IkBα, NF-kB, TREM2, inflammation | [82,83] |
| TAK-242; Resatorvid | TLR4, apoptosis, IL-1β, inflammation | [84,85] |
| Troxerutin | CK-mB, MDA, ROS, ATP | [86,87] |
| Vinpocetine | MAPK, NF-kB, MMP-9, AKT, ROS, Nrf2, HO-1, NQO-1, IL-1β, TNF-α | [88,89] |
| Poria Cocos | ROS, MDA, SOD, LOX-1, Nrf2, HO-1, ERK, oxidative stress | [90,91] |
| Carvacrol | Nrf2, ROS, MDA, SOD, oxidative stress | [92,93] |
| Saururus Chinensis | NF-kB, IL-6, IL-8 | [94,95] |