Green Tea vs. Black Tea Influence on Inflammatory Bowel Disease (IBD)

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Abstract—IBD is chronic inflammation associated with the gastrointestinal tract. The number one symptom of this disease is inflammation. Currently there are various drugs that are anti-inflammatory but have various side effects. So are there any natural approaches to treat IBD? Green tea and black tea could be a potential option. In general tea has about over 4000 bioactive compounds, mainly polyphenols, which are known to influence human health. Tea is known for it's antioxidant and anti-inflammatory properties. With such properties green or black tea are potential options to treat IBD. Through network generation and functional/pathway analysis it was determined that there are many bioactive compounds of both teas that target specific genes found in the IBD pathways. There were eleven black tea targeted genes and nine green tea targeted genes found within the IBD pathway. The other pathways also involved in IBD also showed that there were significantly a lot more black tea targeted genes observed in these pathway. This suggests that black tea could potentially be better as a treatment option for IBD but further research will need to be conducted to determine the regulation of these genes in these pathways.

Index Terms—IBD, Green tea, Black tea, Polyphenols, Targeted Genes, Pathway

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1 INTRODUCTION

Tea is one of the most consumed beverages in the world next to water. In the United States alone, tea can be found in eighty percent of households [1]. Since tea is so common, it is important to know the origin of the tea. Tea is obtained from the leaves of *Camellia sinensis* and depending on how these leaves are processed, a variety of teas can be created: green, black, and oolong tea. This plant usually grows in a moist region where there is sunlight. But why is tea so popular?

Tea is known to contain about 4000 bioactive compounds [2]. These bioactive compounds have shown to influence human health. Tea is known to be a great substance to use against inflammation, reduce DNA damage through antioxidant function, prevent cardiovascular diseases, help the gastrointestinal tract in absorption, prevent tooth decay, and prevent liver, urinary, and prostate cancer [3]. Among different bioactive compounds, it is shown that polyphenols have the largest influence on human health. Polyphenols are natural products with specific structural features (contains aromatic ring, double bonds, and hydroxyl groups) that are attributed to antioxidant and anti-inflammation properties. Specifically, looking at green and black tea, we see an abundance of flavonoids, which are a type of polyphenol. Interesting within this class of flavonoids are catechins from green tea and theaflavins/thearubigins form black tea. There are different types of theaflavins including theaflavin 3-gallate, theaflavin 3-gallate, and theaflavin 3,3-gallate. Similarly, there are different types of catechins as well, which include epigallocatechin gallate, epigallocatechin, epicatechin gallate, and epicatechin. Research has shown that these specific compounds are associated with the health benefits of green and black tea. For example, animal studies has shown that catechins and theaflavins both exhibit antitumor activity [4], anti-inflammatory activity [5], and anti-viral activity [5]. Due to a vast number of bioactivities associated with these polyphenols, it would be difficult to research them all at once, so in the current study anti-inflammatory activity of black and green tea was investigated.

1.1 *Motivation*

IBD is a group of autoimmune diseases that are characterized by inflammation of both the small and large intestine, where elements of the digestive system are attacked by the bodys own immune system [6]. Two major forms of IBD are known as, Crohns disease and Ulcerative colitis. There are a number of signaling pathways involved in inflammation and they include: transcription nuclear factor-kappa B (NF-B) mediated I kappa B kinase complex (IKK) pathways, cyclooxygenase (Cox)-2 and B-cell lymphoma-2 (Bcl-2) activities, and protective programmed cell death pathways [7]. A major gene regulator is the tumor necrosis factor (TNF), which is a proinflammatory cytokine that promotes various cytokines leading to various stages of inflammation leading to IBD.

Inflammation is a major symptom of IBD and anti-inflammatory medications are often the clinical intervention used in the treatment of this disease. However,as with many medications used in the treatment of chronic disease there are side effects. Natural compounds have been suggested as an alternative drug in the treatment of IBD. Using animal models, natural compounds from green and black tea have been shown to significantly down regulate inflammatory related genes TNF-alpha, IL-6, and serum amyloid A [7]. It is also shown that the gene NF-B, active in inflammation state, is inhibited by green tea polyphenols. Similarly, theaflavins present in black tea have been shown to downregulate COX-2, TNF-alpha, iNOS, ICAM-1, and NF-B [5]. Although the review of current literature show various genes are regulated in the animal model of IBD, the mechanism of action of polyphenols in the control of inflammation has not

been completely understood. We hypothesize that there are various bioactive compounds that target the genes involved with the IBD pathway as well as pathways within IBD as well. The over arching goal of this study was to determine how/what biologically active ingredients of tea (green and black), like the polyphenols target the pathways associated with inflammation, are involved in IBD.

2 MATERIALS AND METHODOLOGY

2.1 Data Collection

The bioactive compounds of both green and black tea were obtained from the Tea Metabolome Database. The associated compound identification number (CID) for each compound was obtained from PubChem. The target proteins associated with each compound was obtained from PubChem Bioassay. The genes associated with these target proteins were obtained from NCBI gene.

2.2 Data Reformat

The target proteins obtained from PubChem Bioassay were only provided with their associated compounds not the unique CID identifier. The CIDs were obtained for these compounds through using PubChem's Pugrest to programmatically, through R, download the associated CIDs for a given AID (which is the unique identifier for target proteins). To determine which specific compounds from the original data had specific target proteins, mapping was done through Python programming. In order to determine the gene id's of these target proteins there GeneInfo Identifier(GI) number were obtained through NCBI Entrez Bulk Download. These GI values were then mapped to specific accession numbers to help determine the gene id through Python. With the modified data, the compounds were mapped to their specific targets as well as targets mapped to their genes through Python.

2.3 Network Generation

With these mapped data files the following specific networks were developed in Cytoscape: Tea-Chemical Compound, Chemical Compound-Target Protein, Target Protein-Genes, Tea-Target Protein.

2.3.1 Tea-Chemical Compound

The nodes for the tea were green and black tea and the nodes for the chemical compounds were the list of associated compounds obtained from the Tea Metabolome Database. The association is that X tea contains Y compound.

2.3.2 Chemical Compound-Target Protein

The nodes for the chemical compounds were the list of associated compounds. The nodes for the target proteins were proteins targeted by compounds. The association is that X compound targets Y protein.

2.3.3 Target Protein-Genes

The nodes for the target proteins were proteins targeted by compounds. The nodes for the genes were the genes that are protein. The association is that X protein is a Y gene.

2.3.4 Tea-Target Protein

The Tea-Chemical Compound network and Chemical Compound-Target Protein network were merged to generate a Tea-Target Protein network.

2.4 Function and Pathway Analysis

The genes associated with target proteins of the tea compounds were run through PANTHER to determine the molecular function and examine pathways they are involved in. These genes were then mapped onto the IBD pathway as well as other pathways associated with IBD in KEGG.

3 RESULTS

From a preliminary search, it was determined that the various compounds within these teas have many other properties like antifungal, antioxidant, anticonvulsants, vitamins, and anti-infection. It is important to note that there were no compounds that showed anti-inflammatory properties. It was determined that there were about 622 bioactive compounds in green tea and 412 bioactive compounds found in black tea as shown in Figure 1. There were 156 common compounds found between green and black tea as shown in Figure 1 as the center circle. Now of the black
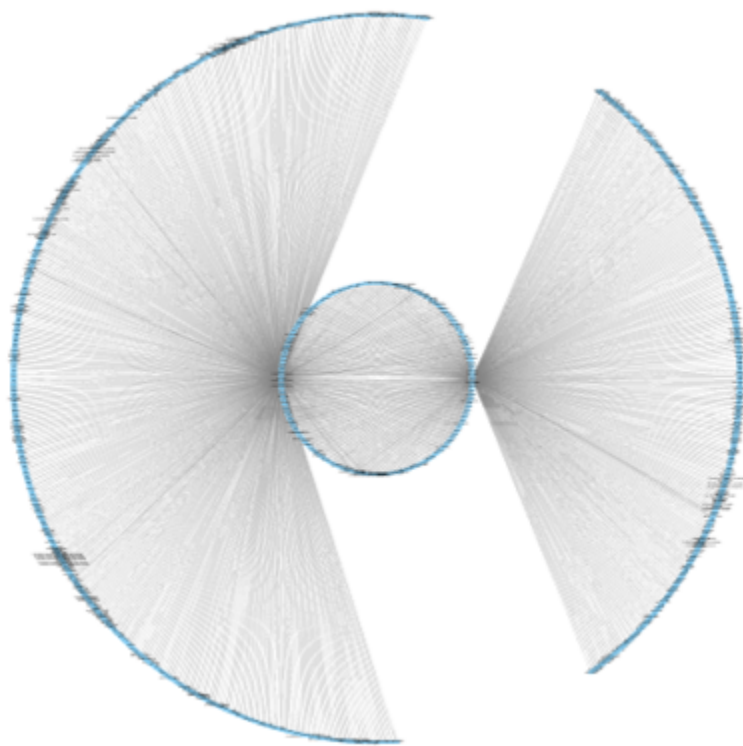

Fig. 1: Green tea and Black tea and their associated bioactive compounds

tea compounds there were a total of 873 target proteins and 673 target proteins for green tea as shown in Figure 2 and 3, respectively. There were 667 common target proteins between green and black tea.

From Figure 4 and 5 it was determined that there 450 black tea target proteins that had an associated gene and 294
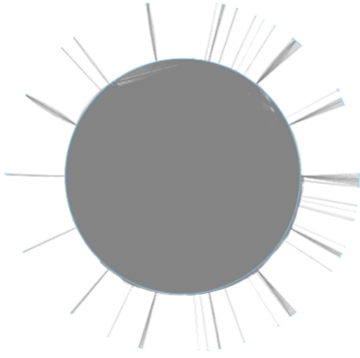
Fig. 2: Black tea bioactive compounds that target specific proteins
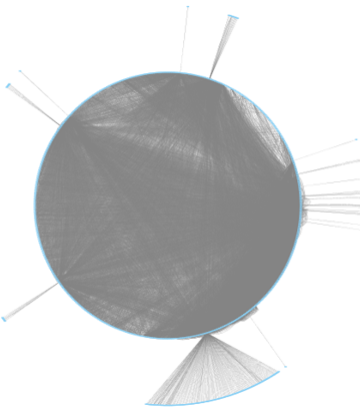

Fig. 3: Green tea bioactive compounds that target specific proteins

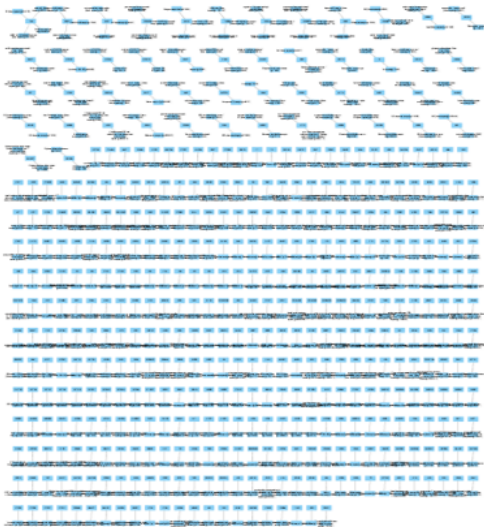for green tea, respectively. There were 293 common genes found.

Fig. 4: Associated genes of Black tea target proteins

These genes for black tea (450) and green tea (294) were then analyzed through PANTHER to determine their molecular functions, separately. From Figure 6 and 7, it can be observed that both black tea and green tea genes have the same molecular functions which include antioxidant
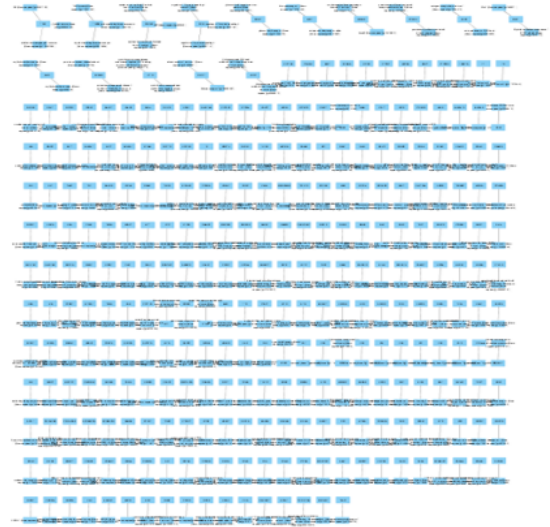

Fig. 5: Associated genes of Green tea target proteins

activity, binding, catalytic activity, receptor activity, signal transducer activity, structural molecule activity, translation regulator activity, and transporter activity.
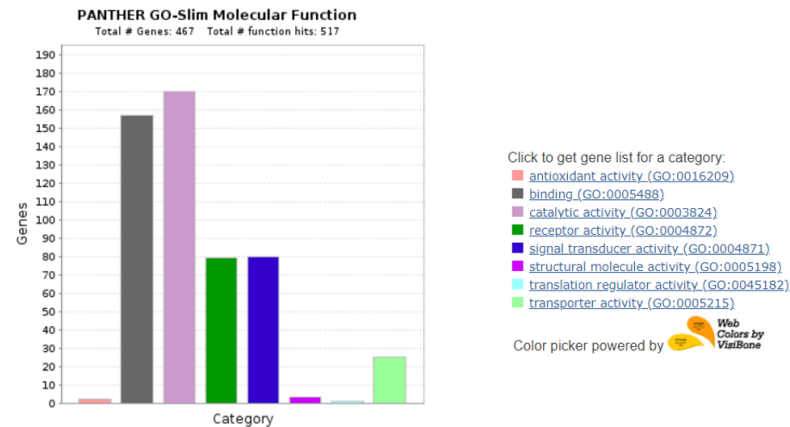

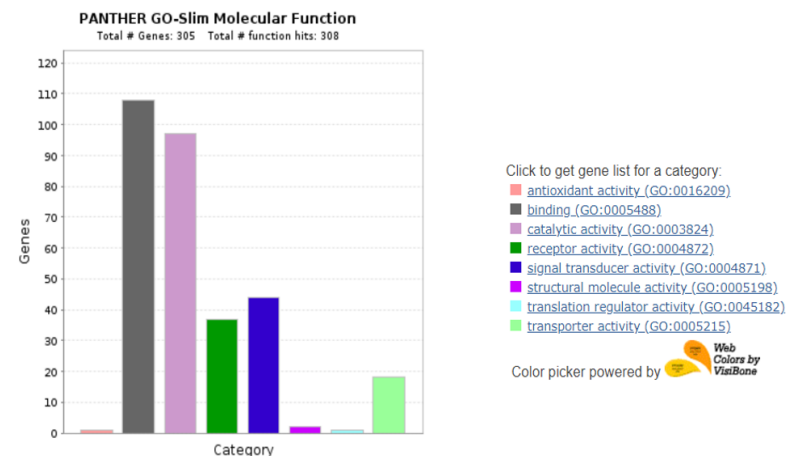Fig. 6: Molecular Functions associated with Black tea genes

Fig. 7: Molecular Functions associated with Green tea genes

Specifically for green tea we see the highest amount of genes associated with a binding function. On the other hand, for black tea we see that the highest amount of genes are associated with catalytic activity. By doing a side by side comparison of the number genes (black tea vs. green tea) , as shown as in Figure 8, associated with a particular molecular function, it can be seen that there a lot more black tea genes with a specific associated function. Through literature research we see that the molecular functions highlighted in red in Figure 8 are associated with IBD pathways.

Functions	Green Tea	Black Tea
Antioxidant activity	1	2
Binding	108	157
Catalytic activity	97	170
Receptor activity	37	79
Signal transducer activity	44	80
Structural molecule activity	2	3
Translation regulator activity	1	1
Transporter activity	18	25

Fig. 8: Comparison of number of Black/Green tea genes with specific molecular functions

Now knowing the molecular functions of these genes, these genes were then mapped onto the IBD pathway from KEGG. The IBD pathway is examining the actually inflammatory response that would occur with associated immune cells. The matched genes for black tea are highlighted in red on the pathway in Figure 11.

The green highlighted are just genes within the IBD pathway that didn't match with the list of genes associated with black tea. The eleven matched genes include: NF-kB, TNF, IFNG, STAT1, AP1, NOD2, IL-1, Smads, STAT3, RORC, and RORA. Most of these genes were found to be associated with molecular functions related to IBD. For example, NOD2 shows binding, catalytic, receptor, translation regulator, and transporter activity. On Figure 12 we can observe the red matched genes for green tea. Again the green highlighted are just genes within the IBD pathway that didn't match with the list of genes associated with green tea. The nine matched genes include: NF-kB, TNF, IFNG, STAT1, AP1, NOD2, IL-1, Smads, and RORC. It is important to note that all nine of these genes were also observed for black tea.

The IBD pathway includes a variety of other pathways such as Toll-like receptor signaling pathway and NOD-like receptor signaling pathway. Figure 9 shows a list of these pathways along with the number of matched genes that were observed for both black and green tea. Again we do see a lot of more genes observed in these pathways for black tea.

With the information of all these genes it's important to note which specific compounds actually led to these genes. In Figure 10, we see a list of bioactive compounds that corresponded with some of these specific genes.

4 DISCUSSION

There are various bioactive compounds within green and black tea that influence genes within the IBD pathway. These bioactive compounds include the polyphenols, phenols, and

Pathway	Green Tea Genes	Black Tea Genes
Toll-like receptor signaling pathway	11	15
NOD-like receptor signaling pathway	15	19
Cytokine-cytokine interaction pathway	8	14
JAK-STAT signaling pathway	7	16
T cell receptor signaling pathway	8	17
Th 17 differentiation signaling pathway	14	22
PI3K/AKT signaling pathway	20	31
NF-kB signaling pathway	9	12
MAPK signaling pathway	23	34
Antigen processing and presentation	4	6

Fig. 9: Pathways found within IBD Pathway and their associated matched genes of Black and Green tea

2H-1-Benzopyran-2-one	2-Methylnaphthalene
2-Methylbutanoic acid	7-Methyl-3-methylene-1,6-octadiene
Heptanoic acid	?-Pinene
Decanoic acid	Ethanol
Dodecanoic acid	Isopropanol
4-Methylphenol	Hexanol
2,6-Dimethylphenol	2-Ethylhexanol
2-(1-Methylpropyl)phenol	Octanol
2-Methoxyphenol	Safrole
2-Methoxy-4-(1-propenyl)phenol	Propanal
1,4-Dimethoxybenzene	2,4-Hexadienal
7-Methylquinoline	Heptanal
Benzonitrile	2,4-Decadienal; (E,E)-form
Ascorbic acid; L-form	2-Methylbenzaldehyde
3,7-Dimethyl-2,6-octadienal; (E)-form	4-Methoxybenzaldehyde
Toluene	Vanilline.
2-Butanol	Acetone
Acrolein	1-Penten-3-one
Pentanal	Ethyl acetate
Butanal	3-Methyl-1-butanol; Ac
2-methylpropanal	2-Methyl-1-propanol
Gallic acid	1-Pentanol or 3-Pentanol
Methyl 2-aminobenzoate	Benzyl acetate
Ethylbenzene	Benzoic acid; Me ester
1-Methylnaphthalene	

Fig. 10: Some bioactive compounds that influenced the IBD and other pathways

acids. It is interesting to see that most of the bioactive compounds from Figure 12 are common compounds that one wouldn't expect to see influence on IBD. Initially, from the data it was shown that many of bioactive compounds had properties such as antioxidant or antifungal, but no anti-inflammatory was observed. As a result one can infer that some of these bioactive compounds are novel in terms of potentially showing anti-inflammatory or inflammatory properties. The reason these could be considered either anti-inflammatory or inflammatory is because we don't know if these compounds would result in the upregulation or downregulation of their associated genes. The literature has shown that genes like TNF, IL-1, and NFB are downregulated by green and black tea.
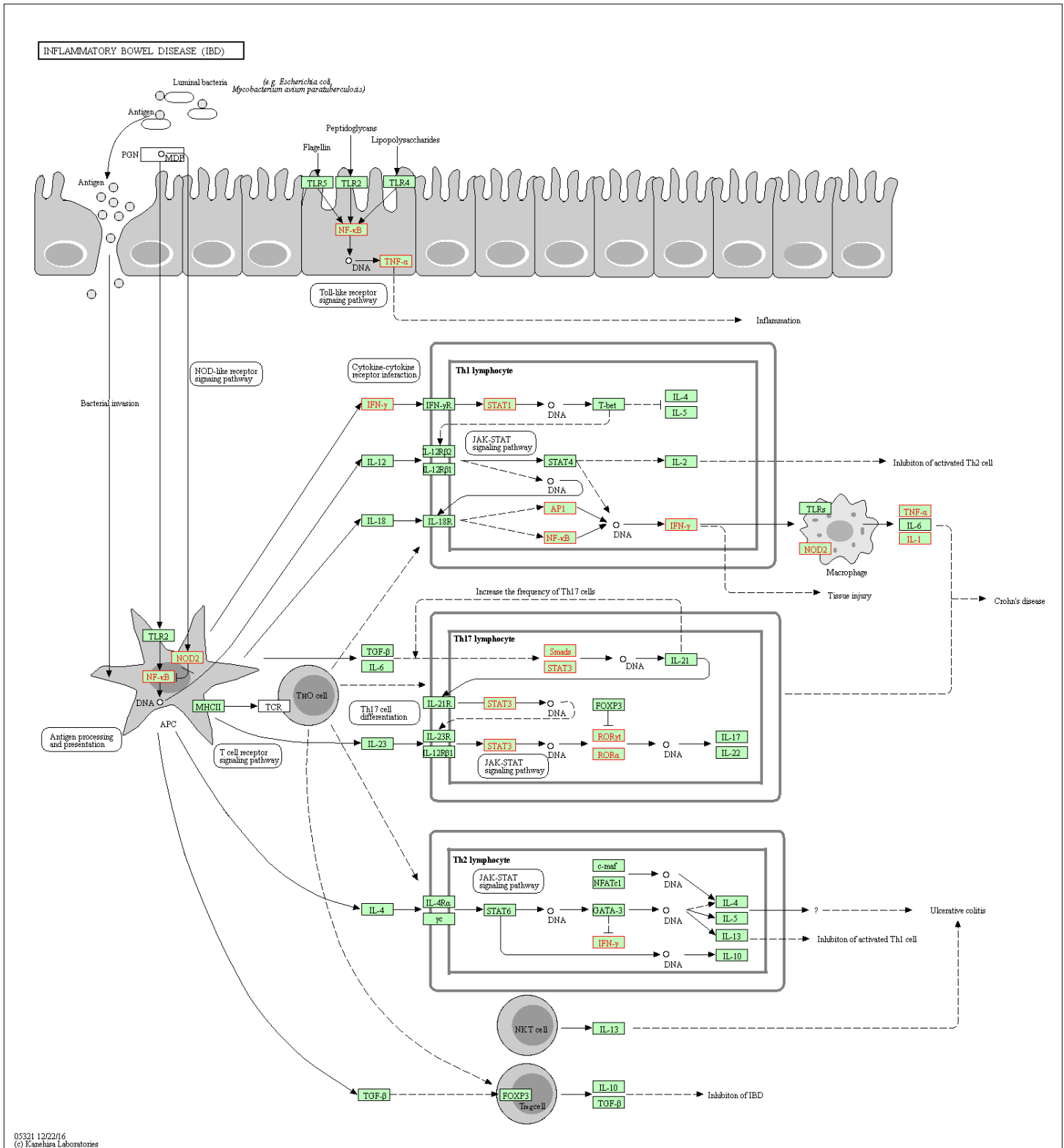
Fig. 11: IBD pathway highlighting matched Black tea genes

Both black and green tea had many overlaps in the target genes observed in the IBD and other pathways as well, but black tea has significantly more target genes observed in the IBD as well as other pathways. This is because there were more genes for black tea compared to green tea to begin with. Overall, this shows us that black tea could have more of an impact on IBD compared to green tea because it targets a lot more genes associated with IBD. Through a literature review, green tea has shown more effects on inflammation. Previously, I believed that green tea had a lot more bioactive compounds and health benefits compared to black tea. But from the data we see that black tea is able to target many
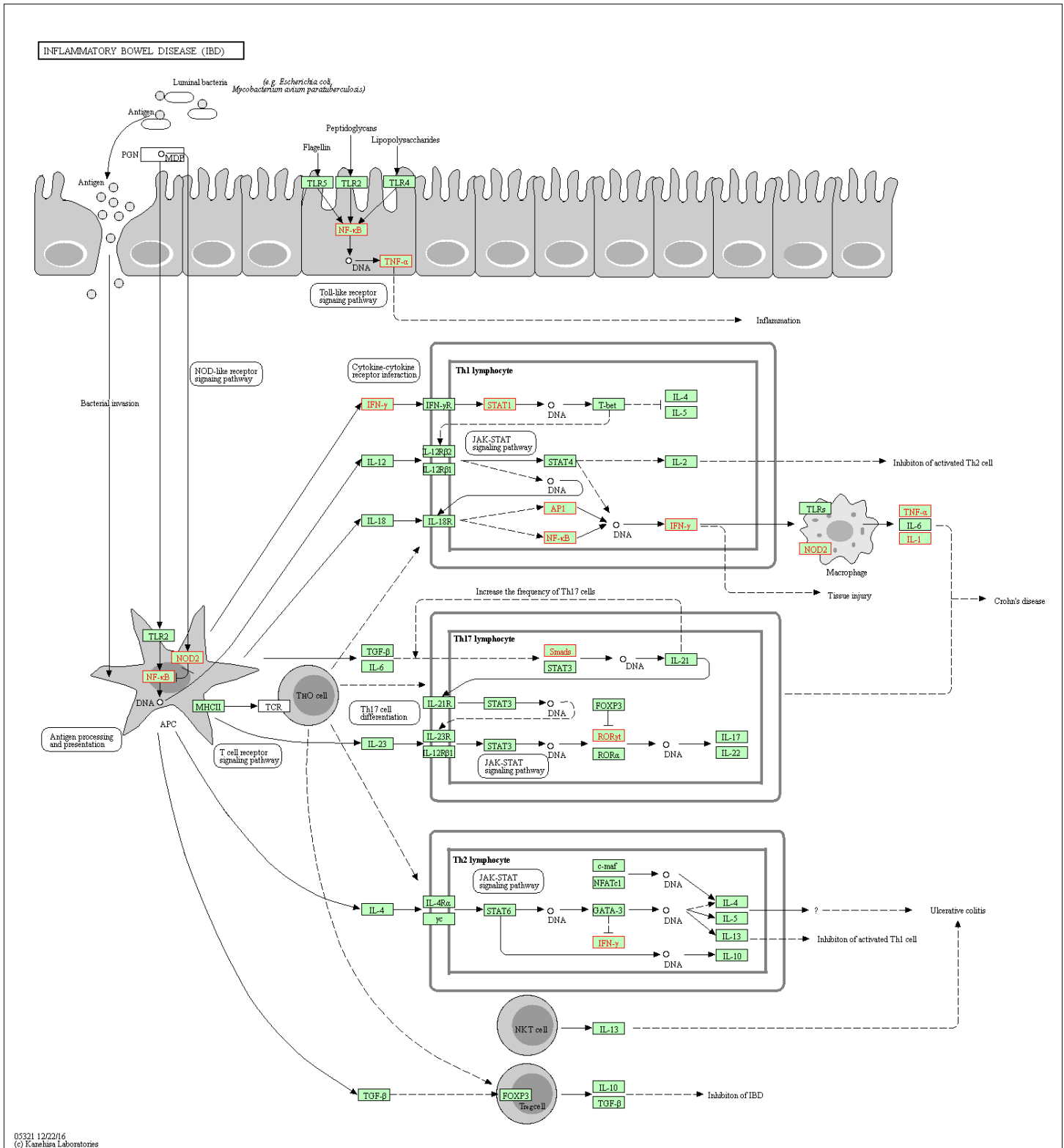
Fig. 12: IBD pathway highlighting match Green tea genes

more genes within IBD compared to green tea.

With the knowledge that there are certain genes that are targeted by the bioactive compounds of both black and green tea there should be further studies to know if these genes are up or down regulated in IBD and its associated pathway or if they inhibit certain processes in the pathway.

This information could potentially help us design certain drugs for treating patients with IBD. The natural approach could truly help individuals who suffer from IBD as they would not have to face the numerous side effects associated with current drug treatment options.

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