

Pathway analysis of the effect of virgin coconut oil on suppressing colonic mucosal inflammation and clinical symptoms in ulcerative colitis

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Abstract

Ulcerative colitis (UC) is an inflammatory disease of the large intestine characterized by ulceration and diffuse mucosal damage. Virgin coconut oil (VCO), with its anti-inflammatory properties, emerges as a potential preventive solution for UC. VCO can be an alternative because it has relatively few side effects compared to chemical drugs. This study aims to determine the effect of VCO on suppressing colonic mucosal inflammation and clinical symptoms of UC through pathway analysis. A model grounded in equations within path analysis emerges as a superior framework compared to regression for elucidating the collective impact of PPAR- γ expression, NF- κ B p65 expression, the quantity of M1 and M2 macrophages, the M1/M2 macrophage ratio, as well as TNF- α , IL-6, and IL-10 levels, and the MCHI score on DAI in UC model mice. Achieving an R²y9 value of 0.998 vastly surpasses the R² value of 0.252 attained through regression analysis. This R²y9 value denotes that the cumulative influence of the mentioned variables on DAI stands at an impressive 99.8%. Drawing from the outcomes of pathway analysis, it is evident that VCO exhibits anti-inflammatory properties in UC model mice. To advance this understanding, future investigations could focus on refining VCO into a medicinal formulation suitable for commercial consumption.

Keywords

Anti-inflammatory, pathway analysis, ulcerative colitis, virgin coconut oil

Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD), which is an inflammatory disease of the large intestine characterized by ulceration and diffuse mucosal damage (Kellermann and Riis 2021). The inflammatory process in UC starts from the rectum and then extends proximally continuously, can involve part or all of the colon, and only affects the mucosa and submucosa layers of the intestine (Ye et al. 2020). The incidence and prevalence of UC are increasing over time throughout the world, and in 2023, the prevalence of UC is estimated to reach 5 million cases worldwide and will continue to increase (Catherine et al. 2023). UC is becoming a global problem when there is an increase in incidence at a young age. Approximately 20% to 30% of patients are diagnosed in childhood or adolescence (Fuller 2019). The highest incidence of UC is found in adolescence, where a quarter of cases diagnosed occur under the age of 18 years (Roberts et al. 2020).

UC in children has broader manifestations and a more aggressive disease course than in adults. Symptoms of UC in children can include abdominal pain, hematochezia, diarrhea, anemia, and systemic symptoms such as anorexia, weight loss, growth retardation, and anxiety (Fuller 2019). At least 30% of pediatric IBD patients experience extraintestinal manifestations within 15 years of diagnosis (Soriano and Ramos-Soriano 2017). The risk of malignancy in children with UC is twice as high as in the general population (Olén et al. 2017). In fact, recent studies show that UC mortality in children is three times higher than in the general population (Ashton et al. 2019). Therefore, UC in children requires serious attention.

Treatment of UC with 5-aminosalicylic acid (5-ASA), corticosteroids, immunosuppressive drugs, and the monoclonal antibody TNF- α is frequently used, but the long-term side effects and high costs encourage the need for preventive efforts to prevent UC in children (Huang et al. 2017). One of the corticosteroids for UC therapy is oral or rectal budesonide (Abdalla and Herfarth 2016). The most frequent adverse effects (AEs; $>1/100$ – $<1/10$ cases) linked to budesonide include psychiatric disorders, blurred vision, palpitations, dyspeptic symptoms, skin reactions like urticaria or exanthema, muscle cramps, menstrual disorders, and Cushingoid features or hypokalemia as a result of effects on the endocrine organs (Iborra et al. 2014). Virgin coconut oil (VCO) is an alternative that can be used to prevent and treat UC with minimal adverse effects.

VCO is extracted from coconut flesh using natural methods without chemical processes such as refining, bleaching, and deodorizing (RBD), with or without heating, so that the beneficial phytochemical content such as polyphenols, tocotrienols, and tocopherols in it can be maintained (Hima et al. 2020). VCO has anti-inflammatory, antipyretic, antioxidant, anticancer, and antimicrobial effects and can act as a neuroprotector and analgesic (Trismayanti et al. 2023). VCO is also able to reduce blood pressure and blood glucose and improve lipid profiles (Ma and Lee 2016). Linoleic acid (LA) is a form of polyunsaturated fatty acid (PUFA) contained in VCO. PUFA is a

natural ligand of PPAR, and linoleic acid is believed to act as a PPAR- γ ligand in the colon, thereby providing an anti-inflammatory effect and maintaining the balance of intestinal immunity (Kuniyasu 2008; Liberato et al. 2012).

Based on the benefits of VCO and the urgency of UC treatment, this research was conducted with the aim of determining the effect of VCO on suppressing inflammation of the colonic mucosa and clinical symptoms of UC model mice through pathway analysis so that VCO can later be used as a functional food to prevent UC, especially in the pediatric population. It is hoped that the research results will provide a scientific basis for administering VCO for safe and efficient UC therapy with effective results, minimal side effects, and relatively economical costs.

Material and methods

VCO extraction

The samples used came from coconuts (*Cocos nucifera*) of the Dalem Mapanget (DMT) variety aged 11–12 months, which were obtained from the Palm Crops Research Institute, Ministry of Agriculture, Manado, Indonesia. VCO is made using the dry method, using the Direct Micro Expelling (DME) method.

VCO is obtained through a dry extraction process based on the DME method outlined by the Asian Pacific Coconut Community (APCC 2009), with several adjustments. In this research, extraction was carried out using the Direct Micro Expelling-Flat Bed Dried (DME-FBD) method, which processes coconut oil using a flatbed drying system (Pradhana et al. 2019). This dry extraction method involves heating coconut seeds under controlled conditions. The grated coconut meat is roasted in several stages: stage 1 between 35 and 49 °C, stage 2 between 45 and 55 °C, stage 3 between 50 and 65 °C, and stage 4 between 60 and 100 °C. This aims to reduce the water content slowly and avoid browning of the grated coconut or case hardening, which causes damage to food ingredients (Tuina et al. 2013; Pradhana et al. 2019). The dried coconut meat is pressed using a modified mechanical jack to produce VCO, which is then separated and purified before being cooled for further use (Ghani et al. 2018).

Treatment VCO

A total of 30 male BALB/c mice aged 6–8 weeks with a body weight of 20–24 grams were divided into five groups. In each treatment group, six repetitions were carried out, where one repetition was used to anticipate drop-out events. The treatment group consisted of: (1) Negative Control Group (KS), which was given mineral water; (2) Positive Control Group (KDSS), which was given 5% DSS; (3) UC Model Group 1 (KL-VCO), which was given 5% DSS and 1000 mg/kgBW/day VCO therapy; (4) UC Model Group 2 (KM-VCO), which was given DSS 5% and VCO 3000 mg/kgBW/day; and (5) UC Model Group 3 (KH-VCO), which was given DSS 5% and VCO 9000 mg/kgBW/day.

Treatment is given for 5 days. Before the mice were sacrificed, clinical symptoms were assessed by measuring the Disease Activity Index (DAI) score. Next, surgery and removal of the colon are performed. Mucosal inflammation was observed histopathologically with hematoxylin-eosin staining and assessed with the Mouse Colitis Histology Index (MCHI) score. The levels of TNF- α , IL-6, and IL-10 were measured using the ELISA method, while the expression of PPAR- γ , NF- κ B p65, and the M1/M2 macrophage ratio were measured using the immunofluorescence method. This research has been carried out as preliminary research (Trismayanti et al. 2023).

The use of experimental animals has been carried out in accordance with the code of ethics, which is marked by the issuance of ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Brawijaya University, with ethical statement number: No. 256/EC/KEPK-S3/09/2021.

Path analysis

Path analysis is the development of multiple regressions. Path analysis is a statistical technique that provides possible direct or indirect causal relationships between a set of variables (Streiner 2005; Kuncoro 2007; Nurmawati 2019). Path analysis prerequisites must be met before the analysis is carried out, including: 1) a minimum data scale of at least an interval scale, and in this study the data scale of all variables analyzed is on a ratio scale; 2) sample data for each response variable must have a nor-

mal distribution, and in this study all response variables have a normal distribution. The response variables that will be analyzed include: a) expression of PPAR- γ (X); b) NF- κ B p65 expression (Y₁); c) number of M1 macrophages (Y₂); d) number of M2 macrophages (Y₃); e) M1/M2 macrophage ratio (Y₄); f) TNF- α levels (Y₅); g) IL-6 levels (Y₆); h) IL-10 levels (Y₇); i) MCHI score (Y₈); and j) DAI score (Y₉).

The first step in path analysis is creating a path analysis model based on theory that describes the relationship between variables. The model is in the form of a path diagram and a system of equations that show cause-and-effect relationships. Statistical analysis was performed with IBM SPSS Statistics 25.0 for Windows. A path diagram was created using SmartPLS 3.0 for Windows. Results are considered statistically significant if the p value is <0.05.

Result

Path analysis model

Pathway diagram model of the relationship between PPAR- γ expression, NF- κ B p65 expression, number of M1 macrophages, number of M2 macrophages, M1/M2 macrophage ratio, TNF- α levels, IL-6 levels, IL-10 levels, MCHI score, and DAI scores in UC model mice given 5% DSS + VCO at doses of 1000 mg/kg/day, 3000 mg/kg/day, and 9000 mg/kg/day are shown in Fig. 1.

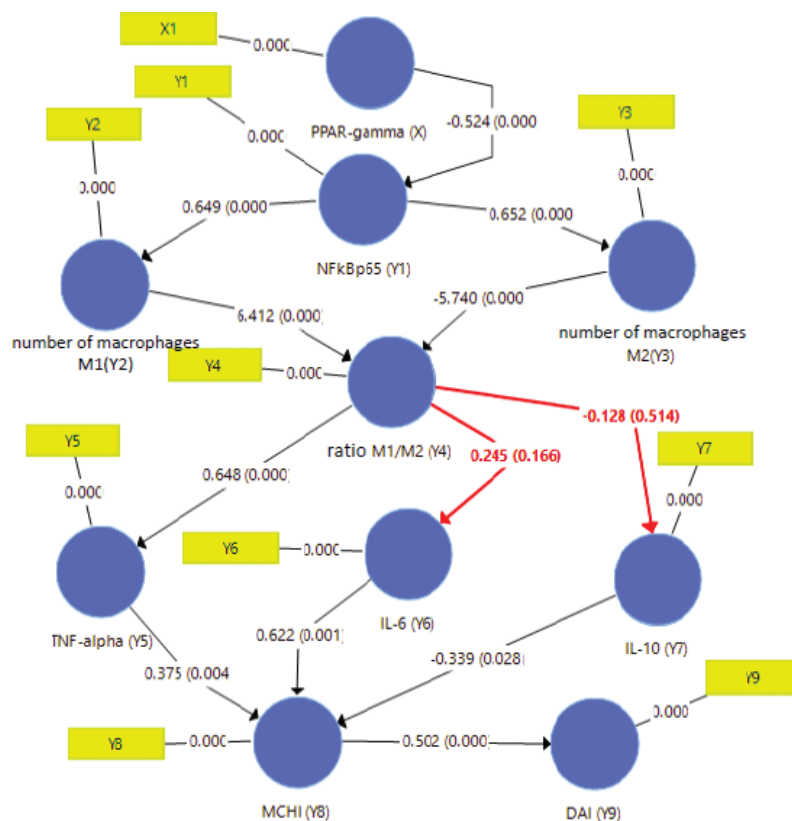


Figure 1. Pathway diagram in the relationship model between PPAR- γ expression (X), NF- κ B p65 expression (Y1), number of M1 macrophages (Y2), number of M2 macrophages (Y3), M1/M2 macrophage ratio (Y4), TNF- α (Y5), IL-6 levels (Y6), IL-10 levels (Y7), MCHI (Y8), and DAI (Y9).

The model presented in Fig. 1 can also be formed into nine equational system models, namely:

$$Y_1 = -0.524X + 0.851e_1 \text{ with } p = 0.000 \text{ and } R_2 = 0.275$$

$$Y_2 = 0.649Y_1 + 0.761e_2 \text{ with } p = 0.000 \text{ and } R_2 = 0.421$$

$$Y_3 = 0.652Y_1 + 0.758e_3 \text{ with } p = 0.000 \text{ and } R_2 = 0.425$$

$$Y_4 = 6.412Y_2 - 5.740Y_3 + 0.319e_4 \text{ with } p = 0.000 \text{ and } R_2 = 0.898$$

$$Y_5 = 0.648Y_4 + 0.762e_5 \text{ with } p = 0.000 \text{ and } R_2 = 0.420$$

$$Y_6 = 0.245Y_4 + 0.970e_6 \text{ with } p = 0.166 \text{ and } R_2 = 0.060$$

$$Y_7 = -0.128Y_4 + 0.992e_7 \text{ with } p = 0.514 \text{ and } R_2 = 0.016$$

$$Y_8 = 0.375Y_5 + 0.622Y_6 - 0.339Y_7 + 0.432e_8 \text{ with } p = 0.000 \text{ and } R_2 = 0.813$$

$$Y_9 = 0.502Y_8 + 0.865e_9 \text{ with } p = 0.000 \text{ and } R_2 = 0.252$$

Model validation

The calculation of the total coefficient of determination is as follows:

$$R^2_{y_9} = 1 - \frac{P^2_{y1e1} + P^2_{y2e2} + P^2_{y3e3} + P^2_{y4e4} + P^2_{y5e5} + P^2_{y6e6} + P^2_{y7e7} + P^2_{y8e8}}{1 - [(0.851)^2 + (0.761)^2 + (0.758)^2 + (0.319)^2 + (0.762)^2 + (0.970)^2 + (0.992)^2 + (0.432)^2 + (0.865)^2]} = 0.998$$

Based on the results of the validity of the model, the value $R^2_{y_9} = 0.998$ is obtained, which turns out to be much greater than the value $R^2 = 0.252$ obtained from the regression results. Thus, the model based on equations in path analysis can be said to be a better model when compared to the model used in regression in explaining the joint influence of PPAR- γ expression, NF- κ B p65 expression, number of M1 macrophages, number of M2 macrophages, M1/M2 macrophage ratio, TNF- α levels, IL-6 levels, IL-10 levels, and MCHI score against DAI score in UC model mice given 5% DSS + VCO doses of 1000 mg/kg/day, 3000 mg/kg/day, and 9000 mg/kg/day. The value $R^2_{y_9} = 0.998$ indicates that the combined influence of the aforementioned variables on DAI is $R^2_{y_9} \times 100\% = 0.998 \times 100\% = 99.8\%$, with other variables that are not yet present accounting for the remaining 0.2% in the model and error/residual.

Direct effect between the variables

The direct effect between variables PPAR- γ , NF- κ B p65 expression, number of M1 macrophages, number of M2 macrophages, M1/M2 macrophage ratio, TNF- α levels, IL-6 levels, IL-10 levels, MCHI score, and DAI score on UC model mice as the effect of giving 5% DSS + VCO doses of 1000 mg/kg/day, 3000 mg/kg/day, and 9000 mg/kg/day is shown in Table 1.

Table 1. Direct Effect Between the Variables.

Variable	Impact on	Effect Coefficient	R Square	p-value
PPAR- γ Expression	NF- κ B p65 Expression	-0.524	0.275	0.000
NF- κ B p65 Expression	Number of M1 Macrophages	0.649	0.421	0.000
Expression NF- κ B p65	Number of M2 Macrophages	0.652	0.425	0.000
Number of M1 Macrophages	M1/M2 Macrophage Ratio	6.412	0.898	0.000
Number of M2 Macrophages	M1/M2 Macrophage Ratio	-5.740		0.000
M1/M2 Macrophage Ratio	TNF- α Levels	0.648	0.420	0.000
M1/M2 Macrophage Ratio	IL-6 Levels	0.245	0.060	0.166
M1/M2 Macrophage Ratio	IL-10 Levels	-0.128	0.016	0.514
TNF- α Levels	MCHI	0.375	0.813	0.004
IL-6 Levels	MCHI	0.622		0.001
IL-10 Levels	MCHI	-0.339		0.028
MCHI	DAI	0.502	0.252	0.000

Model 1: $Y_1 = -0.524X + 0.851e_1$ with $p = 0.000$ and $R^2 = 0.275$

Model (1) shows that there is a significant influence ($p = 0.000$) on the PPAR- γ (X) expression pathway on NF- κ B p65 (Y_1) expression with an influence coefficient of -0.524. Giving 5% DSS + VCO to UC model mice was able to increase PPAR- γ expression, which in turn had an effect on decreasing NF- κ B p65 expression. The percentage influence of PPAR- γ expression on NF- κ B p65 expression was 27.5%. NF- κ B p65 expression in this study was also influenced by other variables besides PPAR- γ expression by 72.5%.

Model 2: $Y_2 = 0.649Y_1 + 0.761e_2$ with $p = 0.000$ and $R^2 = 0.421$

Model (2) shows that there is a significant influence ($p = 0.000$) on the NF- κ B p65 (Y_1) expression pathway on the number of M1 macrophages (Y_2) with an influence coefficient of 0.649. Giving 5% DSS + VCO to UC model mice was able to reduce the expression of NF- κ B p65, which in turn had an effect on reducing the number of M1 macrophages. The large percentage effect of NF- κ B p65 expression on the number of M1 macrophages was 42.1%. The number of M1 macrophages was also influenced by other variables, besides NF- κ B p65 expression, by 57.9%.

Model 3: $Y_3 = 0.652Y_1 + 0.758e_3$ dengan $p = 0.000$ dan $R^2 = 0.425$

Model (3) shows that there is a significant influence ($p = 0.000$) on the NF- κ B p65 (Y_1) expression pathway on the number of M2 macrophages (Y_3) with an influence coefficient of 0.652. Giving 5% DSS + VCO to UC model mice

was able to reduce the expression of NF- κ B p65, which in turn had an effect on reducing the number of M2 macrophages. The percentage influence of NF- κ B p65 expression on the number of M2 macrophages was 42.5%. The number of M2 macrophages was also influenced by other variables, besides NF- κ B p65 expression, by 57.5%.

Model 4: $Y_4 = 6.412Y_2 - 5.740Y_3 + 0.319e_4$ with $p = 0.000$ and $R^2 = 0.898$

Model (4) shows a significant influence ($p = 0.000$) simultaneously on the pathway of the number of M1 (Y_2) and M2 (Y_3) macrophages towards the M1/M2 macrophage ratio (Y_4), with coefficients of influence of 6.412 and -5.740, respectively. The administration of 5% DSS + VCO in UC model mice can decrease the number of M1 macrophages while increasing the number of M2 macrophages, subsequently leading to a decrease in the M1/M2 macrophage ratio. The significant influence of the combined number of M1 and M2 macrophages on the M1/M2 macrophage ratio is 89.8%. The M1/M2 macrophage ratio is also influenced by other variables besides the number of M1 and M2 macrophages by 10.2%.

Model 5: $Y_5 = 0.648Y_4 + 0.762e_5$ with $p = 0.000$ and $R^2 = 0.420$

Model (5) shows that there is a significant influence ($p = 0.000$) on the path of the M1/M2 macrophage ratio (Y_4) on TNF- α levels (Y_5) with an influence coefficient of 0.648. Giving 5% DSS and VCO to UC model mice was able to reduce the M1/M2 macrophage ratio, which then had an effect on reducing TNF- α levels. The large percentage influence of the M1/M2 macrophage ratio on TNF- α levels was 42%. TNF- α levels are also influenced by other variables besides the M1/M2 macrophage ratio of 58%.

Model 6: $Y_6 = 0.245Y_4 + 0.970e_6$ with $p = 0.166$ and $R^2 = 0.060$

Model (6) shows that the M1/M2 macrophage ratio (Y_4) has a very small effect on IL-6 (Y_6) levels ($p = 0.166$), with an effect coefficient of 0.245. When 5% DSS and VCO were given to UC model mice, the M1/M2 macrophage ratio went down. This, in turn, caused IL-6 levels to drop. Although this effect is small and not statistically significant, it can be determined that the percentage influence of the M1/M2 macrophage ratio on IL-6 levels is 6%. Other factors, besides the 94% M1/M2 macrophage ratio, also affect IL-6 levels.

Model 7: $Y_7 = -0.128Y_4 + 0.992e_7$ with $p = 0.514$ and $R^2 = 0.016$

Model (7) shows that the M1/M2 macrophage ratio (Y_4) has a very small effect on IL-10 (Y_7) levels ($p = 0.514$), and that effect is statistically insignificant. When 5% DSS and VCO were given to UC model mice, the M1/M2 macrophage ratio went down. This caused IL-10 levels to rise.

Even though this effect is very small and not statistically significant, it can be determined that the large percentage effect of the M1/M2 macrophage ratio on IL-10 levels is 1.6%. In addition to the M1/M2 macrophage ratio of 98.4%, other factors also affect IL-10 levels.

Model 8: $Y_8 = 0.375Y_5 + 0.622Y_6 - 0.339Y_7 + 0.432e_8$ with $p = 0.000$ and $R^2 = 0.813$

Model (8) shows that the levels of TNF- α (Y_5), IL-6 (Y_6), and IL-10 (Y_7) all have a significant effect on MCHI (Y_8), with effect sizes of 0.375 for IL-6, 0.622 for IL-10, and -0.339 for TNF- α (Y_5). Giving DSS 5% + VCO to UC model mice was able to reduce levels of TNF- α and IL-6 and increase IL-10, which in turn had an effect on reducing MCHI. The large percentage of joint influence of TNF- α , IL-6, and IL-10 levels on MCHI was 81.3%. Other factors besides the 18.7% levels of TNF-, IL-6, and IL-10 affect MCHI.

Model 9: $Y_9 = 0.502Y_8 + 0.865e_9$ with $p = 0.000$ and $R^2 = 0.252$

Model (9) shows that there is a significant influence ($p = 0.000$) on the MCHI path (Y_8) on DAI (Y_9) with an influence coefficient of 0.502. Giving 5% DSS and VCO to UC model mice was able to reduce MCHI, which then had an effect on decreasing DAI. The large percentage of MCHI's influence on DAI is 25.2%. By 74.8%, other factors besides MCHI also have an impact on DAI.

Discussion

Ulcerative colitis is an inflammatory disease of the large intestine characterized by ulceration and mucosal damage (Kellermann and Riis 2021). Inflammatory factors in the body interact to influence this UC condition. The colonic mucosa in UC is characterized by the accumulation of M1 macrophages, which then produce large amounts of inflammatory mediators through NF- κ B activation. Activated NF- κ B is a major heterodimer of p50 and p65 units that can move to the nucleus from the cytosol to facilitate target gene transcription and induce the expression of various proinflammatory genes such as IL-6 and TNF- α (Eissa et al. 2017). Several cytokines, such as IL-4 and immune complexes, can induce the polarization of M2 macrophages into different subclasses. It is known that M2 macrophages can reduce inflammation because they help clear up inflammation by producing IL-10 and other anti-inflammatory cytokines and increasing phagocytosis and efferocytosis (Rószler 2015). Maintaining the balance of M1 and M2 macrophages can be a strategy to prevent UC (Yang et al. 2022).

The peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor protein that makes genes start to be copied during the inflammatory process. Fatty acids and their derivatives, as well as a number of plant extracts, are

among the ligands with various chemical structures that can activate PPAR (Pistis and O'Sullivan 2017). PPAR consists of three subtypes, namely PPAR- α , PPAR- γ , and PPAR- β/δ , with diverse tissue distribution (Decara et al. 2020). PPAR- γ expression was higher in white adipose tissue, colon, spleen, lymphoid tissue, and bone marrow. PPAR- γ is antagonistic to transcription factors such as NF- κ B (Coll et al. 2010; Sobolev et al. 2022). The NF- κ B response to PPAR- γ ligand activity weakens the expression of various colon epithelial cell cytokines such as IL-1 β , IL-6, IL-8, TNF- α , INF- γ , iNOS, COX-2, and chemokines, thereby inhibiting the inflammatory pathway (Annese et al. 2012).

VCO in this study was proven to contain linoleic acid (LA), which is a form of PUFA (Saber et al. 2021). LA is believed to have a role as a PPAR- γ ligand so that it can provide anti-inflammatory effects and maintain intestinal immune balance (Kuniyusu 2008; Liberato et al. 2012). The mechanism of anti-inflammatory effects mediated by PPARs is based on reduced activity of pro-inflammatory transcription factors that regulate the expression of genes responsible for inflammation, such as cytokines, adhesion molecules, and extracellular matrix proteins, as well as increased production of anti-inflammatory molecules (Decara et al. 2020). Giving VCO is better because it is an edible food that we can include in our diets, doesn't require a prescription from a doctor, and doesn't have any negative side effects (Meng et al. 2019).

In this study, administration of VCO will activate the PPAR- γ pathway. Furthermore, PPAR- γ , which is

activated by ligands, will be antagonistic to the NF- κ B transcription factor. The response of NF- κ B to PPAR- γ ligand activity is to significantly weaken the expression of colon epithelial cell cytokines, namely TNF- α and IL-6. Inhibition of TNF- α activates IL-10 through expression from CD4+ T cells, which causes downregulation of NO and ROS production as central to IL-10 protection in colitis model mice (Li et al. 2014). IL-10 causes modulation of the inflammatory cascade, affecting the number of M1M2 macrophages through PPAR- γ activation, thereby preventing the occurrence of UC. Inhibition of TNF- α , inhibition of NF- κ B p65, and an increase in IL-10 significantly influence inflammation in the colonic mucosa based on MCHI, which in turn influences DAI.

Conclusion

Based on the results of the pathway analysis, VCO has an anti-inflammatory effect through the PPAR- γ pathway by inhibiting the NF- κ B transcription factor so that the expression of TNF- α and IL-6 is weakened, which then activates IL-10 and affects the balance of M1 and M2 macrophages. Inhibition of TNF- α and NF- κ B p65, as well as increasing IL-10, can suppress colonic mucosal inflammation seen in the MCHI score, thereby influencing clinical symptoms that can be seen in the DAI score. Further research can be carried out by formulating this VCO in medicinal form so that it can be consumed commercially.

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Supplementary material 1

Ethical approval letter

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