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Article

Serum Metabolomic Profiling for Colorectal Cancer using Machine Learning

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Abstract: Introduction: Colorectal cancer is one of the deadliest diseases with a high prevalence worldwide and is characterized by the appearance of adenomatous polyps in the colon mucosa which are at high risk of developing into colorectal cancer. This study aims to use serum metabolites as promising non-invasive biomarkers for colorectal cancer detection and prognostication. Differences in serum metabolites in patients with adenomatous polyps, colorectal cancer, and healthy controls are considered to be able to support the prognosis of colorectal cancer. **Methods:** Metabolite dataset is taken from the Metabolomic Workbench. Analysis and validation are carried out in silico using machine learning methods. **Results:** From a total of 234 samples, 113 metabolites were found and 5 metabolites; histidine, lysine, glyceraldehyde, linolenic acid, and aspartic acid were identified as the most significant in differentiating the sample groups. CTD analysis showed that aspartic acid and histidine are associated with the biological pathways of colorectal cancer progression and significant metabolites are associated with cancer-related phenotypes. **Conclusion:** The serum metabolites differ in colorectal cancer and healthy control. The significant metabolites can be used as a consideration in selecting colorectal cancer biomarkers, but improvisation is needed to obtain more accurate biomarkers.

Keywords: Serum metabolite, colorectal cancer, machine learning

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1. Introduction

Globally, colorectal cancer is the third most common malignancy and is the second-largest contributor to cancer-related mortality. This is evidenced by the reporting of more than 1.9 million new cases and 935,000 deaths in 2020 caused by colorectal cancer [1]. Several preventive screening and detection methods have been used in the management of colorectal cancer, including the fecal occult blood test (FOBT), fecal immunochemical test (FIT), colonoscopy, sigmoidoscopy, and family history-based risk assessment [2].

The search for good and reliable biomarkers for screening, monitoring, and early detection of colorectal cancer remains challenging. The initial progression of colorectal cancer is the result of an accumulation of genetic changes characterized by the appearance of adenomatous polyps in the colon mucose [3]. Therefore, patients with adenomatous polyps are at increased risk of developing colorectal cancer. However, currently, a non-invasive method for identifying patients with adenomatous polyps and those who have progressed to colorectal cancer with high sensitivity and specificity is not clinically available. Research that describes the molecular phenotype of patients with colorectal cancer

and adenomatous polyps can improve understanding of the pathophysiology of colorectal cancer and provide a strategy for monitoring populations at risk for colorectal cancer [4].

Serum metabolites are promising non-invasive biomarkers for early detection and prognosis of cancer. Serum metabolites can be studied by metabolomics studies, which is one of the "omics" sciences that evaluates metabolites in a biological system. Metabolomics studies use the latest methods to identify differences in metabolites resulting from metabolic changes under specific conditions so that they can generally be used as markers of certain disease progression. Metabolomics analysis uses data in the form of metabolite screening results from high-throughput machines such as Mass-Spectrometry (MS). The screened data has high complexity so that the analysis requires a method with a high level of accuracy, such as the machine learning method [5].

Metabolic changes caused by disruption of crucial metabolic pathways are currently the focus of many cancer studies. A number of studies have profiled the metabolites present in the tissues of colorectal cancer patients [6], but not many studies have focused on identifying biomarkers of metabolites in serum. Therefore, in this study, prediction of biomarkers for colorectal cancer progression was carried out by conducting metabolomic profiling of serum samples using machine learning methods.

2. Result

In this study, metabolite data from the Metabolomic Workbench came from metabolite characterization from human serum using Liquid Chromatography Mass Spectrometry (LC-MS). LC-MS is a combination of liquid chromatography analysis techniques with mass spectrometry detection analysis. LC-MS is able to separate sample components (metabolites) based on polarity differences, which will then the charged ions are detected by a mass spectrometer detector [7]. Data from the Metabolomic Workbench is prepared by ensuring that the sample data is in column and metabolites data is located in the row and data normalization is carried out. The data is then processed using Orange Data Mining with a workflow that can be seen in Figure 1.

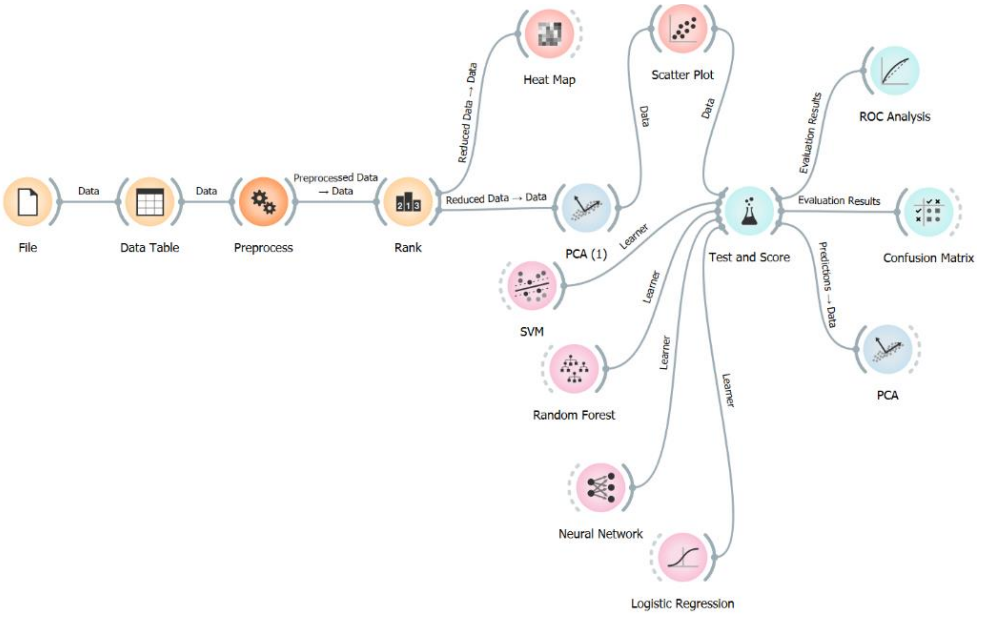
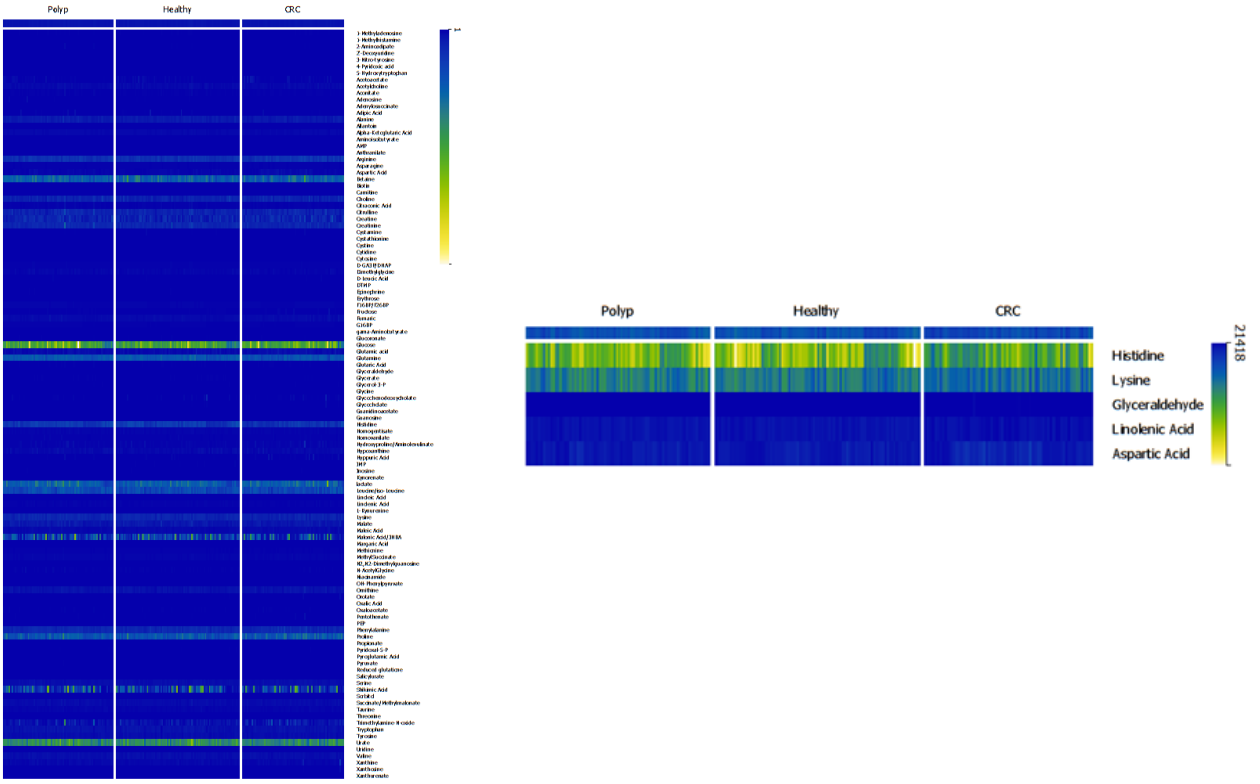


Figure 1. Data analysis *workflow* using Orange Data Mining

The results were visualized in a heatmap plot to see overall differences in metabolite concentrations in the three different sample groups (figure 2a). Based on the heatmap plot, it can be seen that only few metabolites could differentiate the three sample groups. However, after ranking the data based on ANOVA values (figure 2b), a total of 113 metabolites

were obtained and five metabolites with the highest ANOVA values which could significantly differentiate the three sample groups were selected, namely histidine, lysine, glyceraldehyde, linolenic acid, and aspartic acid.



(a) **(b)**

Figure 2. Heatmap plots of concentrations before (a) and after ranking based on ANOVA values (b)

The ranked data is then classified using PCA and visualized using a scatter plot (figure 3). PCA is a technique for extracting patterns from complex and large data. The dataset used is transformed into 2 datasets; one that focuses on variations in proportions and one that focuses on principal components. PC1 includes more variety compared to PC2. The dataset will be visualized with a scree diagram (figure 3) which will illustrate how much variation is obtained from each principal component (PC) [8].

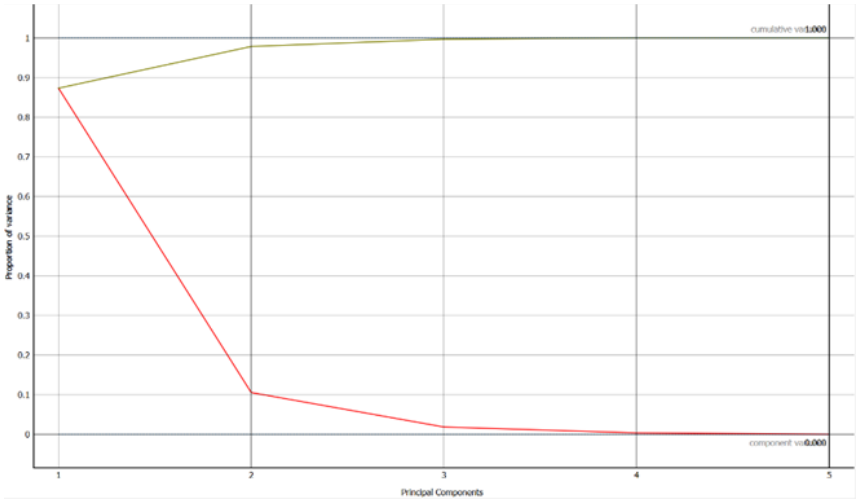


Figure 3. Scree diagram as the result of PCA analysis

In the scree diagram, the y-axis represents the eigenvalues, while the x-axis represents the principal components. Eigenvalues will show how much variation there is. The curve considered ideal if it is steep and sharply curved with the arch as the intersection point and after this intersection the curve will be flat. The red line represents the variation covered by each component, while the green line represents the total variation covered by the component. The red line is seen as a curve that drops sharply at the beginning then curves and flattens. This shows a high level of variation in the first group and a lower level of variation in the second group due to the smaller amount of data. Furthermore, the third group and so on will have fewer variations so that the curve is gradually flatter [9]. The metabolites from datasets of the three sample groups can be distinguished based on the scree diagrams that shows sharp drops in the red line. Then the differences in metabolites in the three sample groups were also visualized using a scatter plot (figure 4).

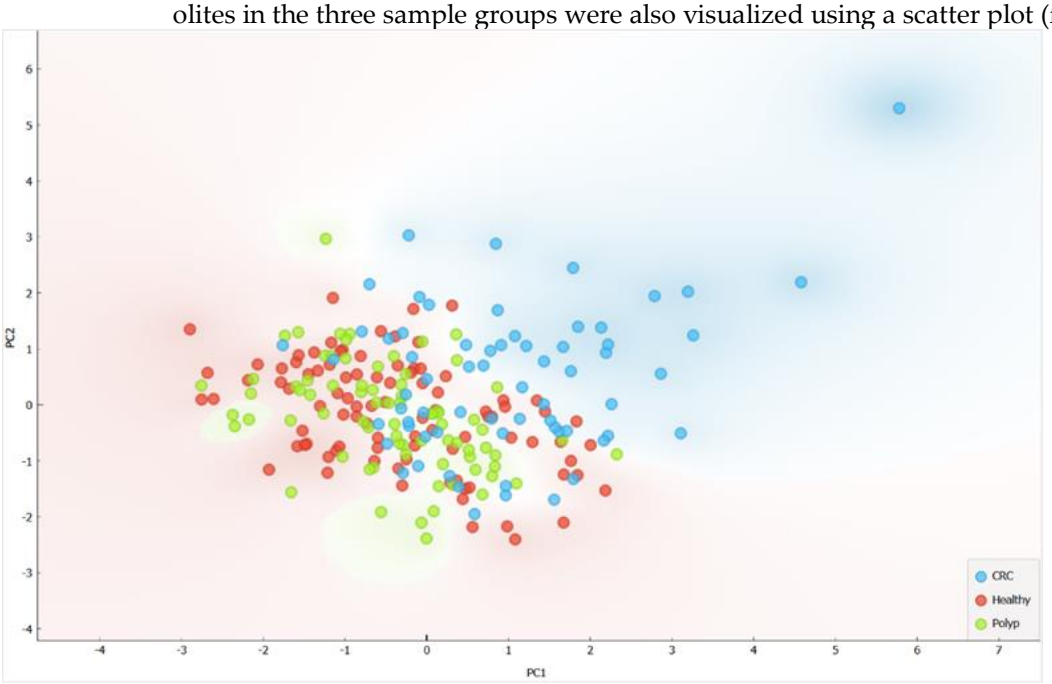


Figure 4. Scatter plot from PCA analysis. Blue: colorectal cancer. Red: healthy control. Green: adenomatous polyps

Apart from being shown in the scree diagram, differences in metabolites in the colorectal cancer group and the other two groups can be seen clearly in the scatter plot. However, the metabolites in the adenomatous polyp group and the healthy controls were similar. This can be seen from the green dots that seem to merge with the red dots even though there are several separate dots.

The results that have been obtained are then cross-validated using machine learning with several different algorithms, namely support vector machine (SVM), random forest, neural network, and logistic regression. The results of cross-validation with machine learning and the confusion matrix for each algorithm can be seen in Figure 5.

Based on the cross-validation results, the highest AUC and precision values were obtained from the neural network algorithm, which is 0.71 and 0.55 respectively. This means that the data used can be accurately, specifically, and sensitively analyzed and compared. The cross-validation results were then plotted into a confusion matrix and it can be seen that based on the neural network algorithm, as many as 70% of the metabolites could differentiate colorectal cancer samples from other groups, then as much as 51.6% of metabolites could distinguish the healthy control group from other groups, and as many as 47 .1% metabolite can distinguish the adenomatous polyp group from other groups.

Model	AUC	CA	F1	Prec	Recall	MCC
SVM	0.663	0.504	0.509	0.519	0.504	0.245
Random Forest	0.684	0.530	0.527	0.526	0.530	0.286
Neural Network	0.710	0.547	0.550	0.555	0.547	0.313
Logistic Regression	0.711	0.538	0.539	0.541	0.538	0.298

(a)

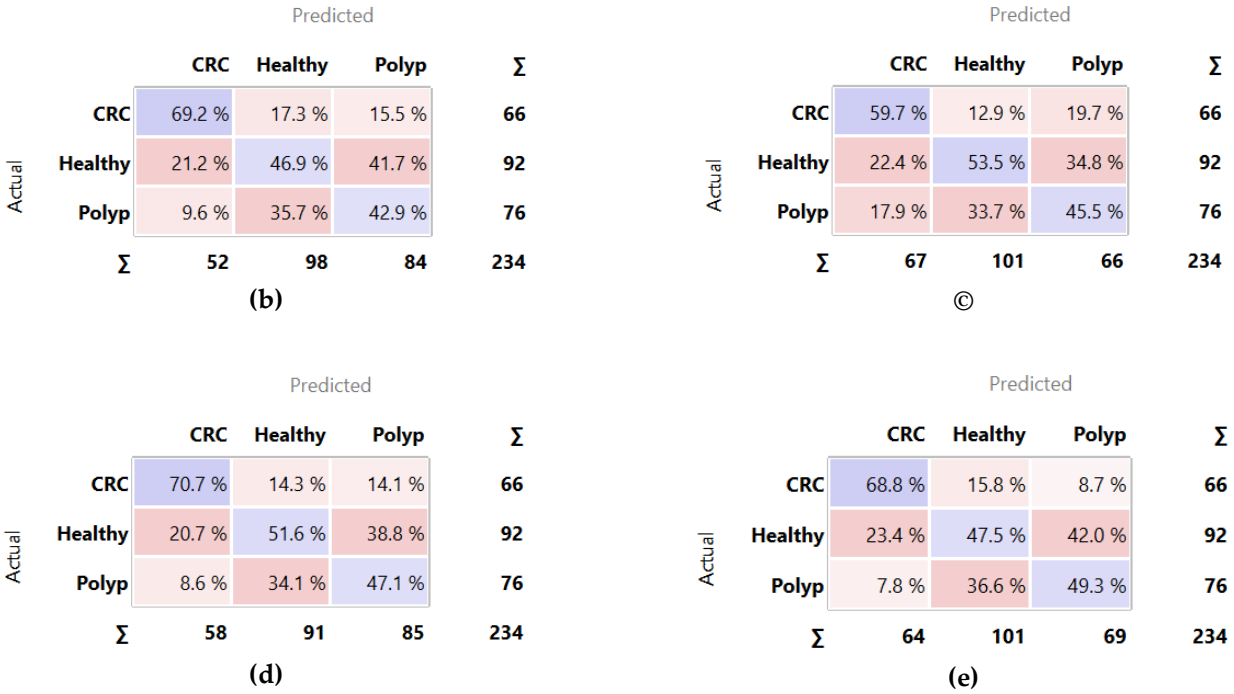


Figure 5. Cross validation results. (a) Machine learning validation results. (b) SVM algorithm confusion matrix. (c) Confusion matrix of random forest algorithm. (d) Confusion matrix of neural network algorithm. (e) Confusion matrix of logistic regression algorithm.

Furthermore, the 5 metabolites that distinguished the three sample groups were used to carry out pathway analysis to determine the correlation between metabolites and colorectal cancer by conducting an analysis on the CTD website. The names of the five most significant metabolites were entered into the query and analyzed by selecting the Pathway association Enriched menu. The results obtained can be seen in table 1.

Metabolites that are directly related to colorectal cancer are aspartic acid and histidine, which are also associated with several biological pathways in colorectal cancer progression, namely the p53 protein signaling pathway and cell proliferation mediated by vascular endothelial growth factor (VEGFR) with a P-Value ranged from 1.19 E-13 through 1.14E-03.

Table 1. Correlation of Metabolites with Biological Pathway

Metabolites	**Biological Pathway**	**Corrected P-Value**
Aspartic acid	Colorectal cancer	1.19E-13
Aspartic acid	VEGFR2 mediated cell proliferation	7.89E-08
Aspartic acid	p53 signalling pathway	3.64E-05
Histidine	Colorectal cancer	2.70E-04
Aspartic acid	VEGF signalling pathway	1.14E-03

Table 2. Correlation of Metabolites with Phenotype

Metabolites	Phenotype	Interaction
Histidine	Metabolic process	Bisphenol F affects metabolic process which affects the abundance of Histidine
Lysine	Alpha-amino acid metabolic process	Malathion results in increased alpha-amino acid metabolic process which results in decreased abundance of Lysine
Lysine	Negative regulation of toxin transport	Lysine results in increased negative regulation of toxin transport which results in decreased import of beta-N-methylamino-L-alanine
Alpha-Linolenic Acid	Apoptotic process	Alpha-Linolenic Acid inhibits the reaction of BCHE protein resulting in increased apoptotic process
Alpha-Linolenic Acid	Cell death	Alpha-Linolenic Acid results in increased cell death
Alpha-Linolenic Acid	Cell population proliferation	Linoleic Acid co-treated with alpha-Linolenic Acid affects the reaction. Fatostatin affects the reaction (BRAF protein affects the susceptibility to Vemurafenib) which affects cell population proliferation
Alpha-Linolenic Acid	Positive regulation of fatty acid biosynthetic process	Pesticides results in increased positive regulation of fatty acid biosynthetic process which results in increased abundance of alpha-Linolenic Acid
Aspartic Acid	Alpha-amino acid metabolic process	Malathion results in increased alpha-amino acid metabolic process which affects the metabolism of Aspartic Acid
Aspartic Acid	Negative regulation of toxin transport	Aspartic Acid results in increased negative regulation of toxin transport then decreased import of beta-N-methylamino-L-alanine
Aspartic Acid	Protein alkylation	Mustard Gas results in increased protein alkylation which results in increased alkylation of TRPA1 protein and alkylation of Aspartic Acid

A correlation analysis of most significant metabolites with phenotype was also carried out. The results of the correlation analysis between metabolites and phenotypes can be seen in table 2. It can be seen that phenotypes associated with histidine are cell metabolic processes related to the interaction of histidine with bisphenol F. Phenotypes related to lysine metabolites are amino acid metabolic processes and negative regulation of toxin transport. Phenotypes related to linolenic acid are processes of apoptosis, cell death, cell proliferation, and fatty acid biosynthesis. The phenotype that correlates with aspartic acid is negative regulation of toxin transport and protein alkylation. However, from the search

for phenotypes related to metabolites, no phenotypes associated with glyceraldehyde were found.

3. Discussion

Histidine has been reported to be increased in colorectal cancer and is associated with a poor colorectal cancer prognosis. Histidine from food is converted by histidine decarboxylase to the biogenic amine histamine, a signaling molecule that mediates the acute inflammatory response by binding to specific receptors. Histidine decarboxylase activity is upregulated in tumor cells and is associated with increased cell proliferation and angiogenesis [10]. Histidine is reported to have a synergistic antitumor effect. Histidine supplementation combined with administration of antifolate chemotherapeutic agents such as methotrexate can reduce tumorigenesis in experimental animals with leukemia [11]. In addition, administration of histidine combined with sorafenib reduced the expression of tumor markers related to glycolysis (GLUT1 and HK2), inflammation (pSTAT3), angiogenesis (VEGFB and VEGFC), stem cells (CD133), metastasis (Snail/slug), and migration of cells [12].

Several major proteinogenic amino acids such as alanine, tyrosine, aspargine, aspartic acid, valine, glutamic acid, glycine, histidine, and isoleucine were identified to be dysregulated in colorectal carcinoma patients. The main energy pathways that are disrupted are the glycolytic pathways known as the Warburg effect, as well as amino acid metabolism. Amino acids are catabolized to meet the nutritional needs of cancer cells and serve as precursors for synthesizing cancer cell nucleotides so that they can grow rapidly with excessive amounts. Amino acids are also broken down to synthesize glutathione which can counteract the increase *Reactive Oxygen Species* (ROS) during cancer cell proliferation or used as a transcriptional or epigenetic regulator to trigger the process of cancer development [13].

Aspartic acid is an amino acid produced from oxaloacetate via transaminase. Changes in serum levels of amino acids observed in cancer patients are closely related to the nutritional requirements for cancer cell development. The amino acids histidine, tyrosine and cysteine (cysteine + cystine), have higher serum levels in patients with colorectal cancer stage 0-2 compared to stage 3-4. While the level of serum lysine significantly lower in stage 3-4 colorectal cancer patients compared to healthy controls. In contrast, serum levels of several amino acids including aspartic acid were significantly increased in colorectal cancer patients with stage 3-4 compared to colorectal cancer patients with stage 0-2. In previous studies, various amino acids including aspartic acid showed higher levels in colorectal tumor tissue than in normal colorectal tissue [14].

In the progression of colorectal cancer, disruption of the function of the p53 protein is an important pathway because it is closely related to colorectal cancer carcinogenesis and cell transformation from adenoma to carcinoma. The p53 protein is a protein expressed by the TP53 gene which is a tumor suppressor gene that plays a significant role in cellular activities, namely the cell cycle, DNA repair, and cell apoptosis. p53 will also respond if there is oxidative stress and abnormal cell proliferation. In addition, in damaged cells, p53 functions to stop the cell cycle until the cell can be repaired. When p53 dysfunction occurs, the likelihood of developing colorectal cancer from an adenoma to a carcinoma increases. The high activation of cell proliferation is caused by a mutation in the p53 gene. In addition, mutations in p53 cause p21 (WAF1) as a tumor suppressor protein not to be expressed so that DNA protection and repair during the cell cycle does not occur [15].

P53 also acts as an inhibitor of angiogenesis and metastasis in cancer cells. p53 partially activates the epithelial mesenchymal transition (EMT) which results in suppression of E-cadherin synthesis with the help of Slug or Twist, which is a transcription factor that controls embryonic development in EMT. The suppression of E-cadherin is closely related to the development of metastases in cancer. In addition, regulation of proangiogenesis factors will be carried out by p53 to suppress angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and increasing the production of Thrombospondin (TSP) as

an angiogenesis inhibitor so that its antiangiogenic properties can be used to inhibit angiogenesis [16].

There are several mutagens that increase the risk of developing cancer. One of them is Bisphenol F, which also shows in correlation with histidine and colorectal cancer. Bisphenol F somehow correlated in increased levels of histidine. In breast cancer, bisphenol F has an estrogenic effect and is found in canned food, plastic, food packaging, and plastic utensils. Mechanistically, bisphenol binds to the estrogen receptor (ER) and activates the expression of genes associated with cell proliferation and breast cancer [17].

The limitation of this research includes the lack of datasets used. To improve this, additional datasets may be needed as it will greatly help increasing the AUC scores when validated. The result of this research can be used in further works such as to study or to confirm the mechanism of interactions of biochemical pathways under several conditions—including cancer, to clarify the mechanisms of defense between the normal and the cancer cells, and to explore more about new metabolites with various activities that correlates with colorectal cancer.

4. Materials and Methods

4.1 Obtaining Metabolite Data from Metabolomic Workbench

Colorectal cancer metabolomic data used in this study were obtained from the Metabolomic Workbench (https://www.metabolomicsworkbench.org/) by entering the keyword "colorectal cancer" in the query section. Then a thorough data search will be carried out by the search engine and the search results will be displayed on the view menu. Data filtering was done by selecting the species *Homo sapiens* and setting the data collection time to the latest to reduce bias. The selected data is the result of LC-MS spectrometry readings with Project ID PR000226 and Study ID ST000284. The data consisted of numerical screening data showing concentrations and types of metabolites obtained from human blood serum from a total of 234 samples categorized into three research subject groups; 66 patients with colorectal cancer (CRC), 76 patients with adenomatous polyps (Polyps), and 92 healthy controls (Healthy).

4.2 Biomarker Prediction using Orange Data Mining

The data obtained from Metabolomic Workbench is in .txt format. Data then converted to .xls format and was organized by placing sample data in rows and metabolite data in columns before being analyzed with Orange Data Mining. The imported data then being normalized. Furthermore, data reduction was carried out by sorting the data based on the ANOVA test to identify the metabolites that had the most significant differences between the sample groups and the results were visualized into heatmap plots. Five metabolites with the highest ANOVA score were taken and continued with a classification process based on variations in metabolite concentrations using an unsupervised statistical model, namely Principal Component Analysis (PCA). Furthermore, the results of the classification are visualized using a scatter plot.

4.3 Machine Learning Cross-validation using Orange Data Mining

Cross validation was performed using machine learning with four different algorithms; logistic regression, random forest, support vector machine (SVM), and neural network. Data validation was carried out by analyzing the AUC parameters and the confusion matrix specifically the values of sensitivity, specificity and accuracy were taken into account.

4.4 Correlation of Metabolites and Phenotype using CTD

Phenotypic analysis related to metabolites was performed using the Comparative Toxicogenomics Database or CTD (http://ctdbase.org/tools/batchQuery.go). The analysis was carried out by entering the list of metabolites from the classification and validation

results into the query by selecting the Chemicals input type. Then the type of data to be obtained is selected, namely Phenotype associations Curated data. The results of the analysis was then downloaded. The data obtained has a .txt format and needs to be converted to .xlx format to be analyzed..

4.5 Correlation of Metabolites and Pathway using CTD

Metabolites can also be associated with metabolic pathways. Analysis of the correlation of metabolites with metabolic pathways was performed using the Comparative Toxicogenomics Database or CTD (http://ctdbase.org/tools/batchQuery.go). The analysis was carried out by entering the list of metabolites from the classification and validation results into the query by selecting the Chemicals input type. Then select the type of data to be obtained, namely Pathway associations Enriched data and download the analysis results. The data obtained has a .txt format and needs to be converted to .xlx format to be analyzed

5. Conclusions

Metabolomics studies carried out using a machine learning approach can be used to differentiate serum metabolites in patients with adenomatous polyps, colorectal cancer, and healthy controls who are considered capable of supporting the prognosis of colorectal cancer. Metabolite data were obtained from the Metabolomic Workbench with Project ID PR000226 and Study ID ST000284. Identification and validation of the data was carried out in silico using machine learning methods with Orange Data Mining software. From a total of 234 samples, 113 metabolites were found and 5 metabolites were identified as the most significant in differentiating the sample groups, namely histidine, lysine, glyceraldehyde, linolenic acid, and aspartic acid. CTD analysis showed that aspartic acid and histidine are associated with the biological pathways of colorectal cancer progression, they are the p53 protein signaling pathway and cell proliferation mediated by vascular endothelial growth factor (VEGFR). These five metabolites are also associated with several cancer-related phenotypes. The results of the analysis can be used as a consideration in selecting colorectal cancer biomarkers, but repetition and additional samples are needed to obtain more accurate biomarkers.

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Conflict of Interest Statement : None declared.

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