

Compound Molecules of Network Pharmacology-Based of Tamarillo (*Cyphomandra betacea* Cav.) and the Potential as Noodle for Type 2 Diabetes Mellitus Treatment

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ABSTRACT

Consuming noodles excessively is not good for health because it contains high trans fat, which can cause diabetes mellitus (DM) as a disease with a high prevalence, especially type 2 DM, as much as 95% in Indonesia. Tamarillo (*Chypomandra betacea* Cav.) can potentially reduce blood glucose levels and restore adipokine regulation to prevent insulin resistance in type 2 DM. This study aims to determine the formulation and potential of tamarillo compounds into noodle products named "Chypotes (Chypomandra Antidiabetes) Noodle" as an alternative food for type 2 DM patients. The methods used are noodle formulation, organoleptic test, hedonic test, and network pharmacology. Based on the results of an organoleptic test, Chypotes Noodle has a chewy texture, a distinctive smell, yellow colour, and a slightly sour tasteless taste typical of Tamarillo. Based on the results of the hedonic test, 30 respondents chose the like and very like options in filling out the questionnaire with a percentage of 80-90%. Based on the Network Pharmacology of Tamarillo shows that 150 of the 365 target proteins of Tamarillo are involved in the biological processes and signaling pathways of type 2 diabetes mellitus, with 75 target proteins locking and interacting. Compound Molecules of Tamarillo, such as six bioactive components of the hydroxycinnamic acids group, have activity in type 2 DM and affect the biological processes and signaling pathways of type 2 DM against ADIPOQ, TNF, and INS. Therefore, Tamarillo can potentially be used as an alternative food product in the form of noodles for type 2 DM treatment.

Keywords: Chypotes Noodle; Hydroxycinnamic Acids; Network Pharmacology; Tamarillo; Type 2 DM

INTRODUCTION

Noodle is a type of flour-processed food famous and favored by various levels of Indonesian society of various ages (Jannah & Ichda, 2021). Noodles, as one of the food products made from wheat flour, contain many carbohydrates that provide an energy supply for the body, so they can be used as an alternative food to replace rice (Andayani, 2022). The varied taste and speed of presentation make people depend on noodles. Data from the *World Instant Noodle Association* (WINA), instant noodle consumption in Indonesia increased by 4.98% to 13.27 billion packs in 2021 compared to the previous year. This high case of consumption causes Indonesia to occupy the second position in the world after China in the instant noodle consumption category, with a total consumption of 43.99 billion packs in 2021 (Solicha & Purnamasari, 2023). However, of course, excessive consumption of noodles is not good for health, especially dry instant noodles, because, through the frying process, they contain high trans-fat,

where trans-fat can cause an increase in cholesterol and other diseases such as diabetes as a disease with a high prevalence in Indonesia (Wulan, 2021).

The prevalence of diabetes mellitus (DM) continues to increase in Indonesia. Based on data from the *International Diabetes Federation* (2019) estimates an increase in DM prevalence globally from 9.3% in 2019 to 10.2% in 2030 and an increase to 10.9% in 2045. The most common and commonly found DM is type 2 DM, as much as 95% in Indonesia (Tandra, 2021). The causes of type 2 diabetes are unhealthy lifestyles, imbalances in dietary arrangements, and lack of physical activity; type 2 DM attacks various age groups with a risk of 36% in the age group of <45 years. Then, the most vulnerable group is the age of >45 years, at a risk of 64% (Chandra et al., 2020). Generally, type 2 DM patients must control their diet with foods that are low in fat, have much fiber, and avoid instant foods such as noodles because noodles can cause an increase in a glycemic index or sugar content (Febricia et al., 2020). Therefore, alternative noodles from natural ingredients that are more friendly to health, especially for type 2 DM patients,

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Table I. Nutritional Content of Tamarillo per 100 g

Composition	Sum
Water	80-90 g
Protein	1.4-2 g
Fat	0.1-0.6 g
Carbohydrates	10.3 g
Fiber	1.4-4.7 g
Vitamin A	540-560 μ
Vitamin E	2 mg
Vitamin C	15-42 mg
Calorie	48 Cal
Calcium	0.28-0.38 mg

Source: (Devi et al., 2018)

Table II. Tamarillo Noodle Formulation

Material	Sum
High protein flour	300 g
Tamarillo	100 g
Egg	55 g
Salt	10 g

are essential. An alternative ingredient that can be used is tamarillo.

Tamarillo is a potential food commodity because it has many benefits that are not widely known by the public; Tamarillo (*Cyphomandra betacea* Cav.) is a type of eggplant family plant (*Solanaceae*) originating from New Zealand. Tamarillo is famous for its low-calorie and low-fat content with other advantages, such as thick yellowish flesh wrapped in a thin membrane that is easy to peel off, sour fruit taste, and plum-like texture. The population of this plant has been found in Indonesia, and it is especially easy to grow in the highlands (Sari et al., 2018).

The nutritional content of tamarillos is varied and beneficial for body health, such as vitamins A, C, and E (Febricia et al., 2020). Every 500 mg of tamarillo contains several complex nutrients such as sugar (0.46), crude fiber (1.98), vitamin C (0.0716), anthocyanins (122.57), and pH (5.9) (Suzanna et al., 2019). In addition, based on Devi et al., (2018) tamarillo contains anthocyanin-type flavonoids, one type of antioxidant source that can be used to minimize oxidation reactions and ward off free radicals. Tamarillo plays a role in reducing blood glucose levels in Type 2 DM patients, primarily because of the content of polyphenols (anthocyanins, flavonoids, phenols) as antioxidants or *Reactive Oxygen Species* (ROS) in

tamarillo, which can restore adipokine regulation to prevent insulin resistance and triglyceride production in adipose tissue (Berawi & Asvita, 2016).

The processing of tamarillo into noodles is a form of health technology in food innovation based on natural ingredients. This development will undoubtedly have an impact on two things, namely the cultivation and processing of tamarillo plants in Indonesia and even the development of household industries, and have an impact on healthy food innovation as an alternative staple food for type 2 DM patients. The formulation of tamarillo noodles is made simply using the formulation of making noodles, in general, to facilitate application in the community sustainably. In addition, the sour taste of tamarillo causes tamarillo to be disliked by the public for direct consumption, so it is necessary to make food innovations (Suzanna et al., 2019).

Parameters test Parameters are carried out using network pharmacology, which is a method that uses integrated network biological systems and computer analysis technology to ascertain the active components and mechanisms of an active ingredient with target proteins (Tjandrawinata et al., 2022). The network pharmacology is used to investigate the molecular mechanisms of tamarillo that play an essential role in reducing insulin

Table III. Result of Organoleptic Test

Parameters	Information
Texture	Supple
Smell	Distinctive
Color	Yellow
Flavor	Tasteless with a slight sourness typical of Tamarillo

Table IV. Nutritional Content (a) Tamarillo Noodles per 100 g (b) Instant Noodles per 85 g

(a) Tamarillo Noodles per 100 g	
Kandungan	Jumlah
Protein	9,65 g
Lemak	2,25 g
Karbohidrat	59,02 g
Serat	2,65 g
Vitamin A	27,6 µ
Vitamin E	0,5 mg
Vitamin C	5 mg
Sodium	19,3 mg
Kalsium	19,6 mg
Total Energi : 301,3 Kcal	
(b) Instant Noodles per 85 g	
Kandungan	Jumlah
Protein	9 g
Lemak	18 g
Karbohidrat	66 g
Serat	3 g
Vitamin A	1,2 g
Vitamin C	1,5 g
Gula	7 g
Sodium	900 mg
Kalsium	1,9 g
Total Energi : 460 Kcal	

resistance in patients with type 2 diabetes. The computational approach to this method can accommodate big and fast data and promising results for studying an active ingredient, in this case, tamarillo (Hilal et al., 2016).

MATERIALS AND METHODS

Materials

The materials used in this study are high-protein flour, tamarillo, eggs, tamarillo compound components, and GeneCards (<https://www.genecards.org>).

Tools

The tools used in this study include scales, noodle printing tools, Cytoscape v3.9.1 (<https://cytoscape.org>), DisGeNET (<https://www.disgenet.org>),

(<https://www.string-db.org/>), and Kyoto Encyclopedia of Genes and Genomes (KEGG) *PATHWAY* (<https://www.genome.jp/kegg/pathway.html>).

Method

Making Tamarillo Noodles

Tamarillo was thoroughly washed, then peeled and separated from the seeds. The tamarillo and other ingredients were weighed as much as needed according to the formulation. Tamarillo was blended until smooth, then mixed with other ingredients until it formed a flat and smooth dough. The next step was to mold the dough using a noodle printer. The difference between this tamarillo noodles formulation with ordinary noodles is the distinctive taste and nutritional content of tamarillo and the use of high protein flour to increase the nutritional content.

How to Serve

To serve tamarillo noodles, prepare tamarillo noodles, heat water until it boils, cook the noodles for 1 minute, and drain. Then, add seasonings according to taste and can be served dry or gravy.

Organoleptic Test

Organoleptic test or sensory test is a way of testing using human senses as the main tool to determine the characteristics of a sample which includes color, aroma, texture, and taste (Khalisa et al., 2021). Organoleptic tests were conducted on 30 respondents before carrying out the hedonic test. The test used the senses of sight, touch, smell, and taste. In this case, the respondents explained the organoleptic of tamarillo noodles (color, texture, aroma, and taste).

Hedonic Test

The hedonic test is a type of test in which respondents or volunteers are asked to express their responses on a questionnaire about their likes or dislikes for a product at a level (Sartika et al., 2020). Hedonic tests were conducted on 30 respondents using questionnaires. Testing was carried out voluntarily on tamarillo noodle products by asking respondents' responses regarding taste, color, aroma, texture, and total acceptance of tamarillo noodle products that have

been served. The favor-dislike assessment is a hedonic scale (Carsidine & Dwiyantri, 2022). The hedonic test scores of the panelists started from 1 (disliked very much), 2 (disliked), 3 (liked quite a bit), 4 (liked), and 5 (liked very much).

Network Pharmacology Test

Collection and screening of bioactive components of Tamarillos

The components of the bioactive compounds of tamarillo were obtained based on the results of a literature study review from other scientific research indexed by *Google Scholar* with the keyword "*Cyphomandra betacea* compound". Based on comparing literature studies, the chosen components are high levels and dominant.

Collection and screening of Tamarillo-related target proteins

Target proteins and genes associated with type 2 DM were obtained from *GeneCards* (Permatasari et al., 2021). The results obtained from *GeneCards* are limited to targets that have a relevance value of ≥ 10.00 , where this value is

considered to meet database standards (Tjandrawinata et al., 2022).

Collection and screening of disease-related target proteins and creation of target networks

The next step is the exploration of target genes associated with type 2 DM using *DisGeNET*. *DisGeNET* collects disease target data by searching a database that collects information about the relationship between proteins and disease targets (Rosyadah et al., 2017). The next step is creating a target network related to tamarillo collected into a target-component network visualized through a similarity network using *Cytoscape* v3.9.1. The target protein and bioactive components of tamarillo are represented as "nodes" (Qomariasih et al., 2016), and the interaction between the two proteins as "edges". The more essential proteins a component targets, the more it can be designated as an essential component (Tjandrawinata et al., 2022).

Creation of protein-protein interaction network (PPI Network) and enrichment analysis

The gene target junction of active ingredient and disease was selected for further analysis using the platform (*STRING*). PPI networks are built using common target proteins with a minimum required interaction score of 0.400. PPI network analysis was used to investigate biological activity by examining functional annotations of *gene ontology* (GO) and *Kyoto Encyclopedia of Genes and Genomes* (KEGG) enrichment of protein pathways and their function in signal transduction (Tjandrawinata et al., 2022).

Data Analysis

Data analysis from this study's content test and characteristic evaluation are arranged descriptively with a theoretical approach. For test results, content analysis data obtained from the network pharmacology test based on four stages, namely: collection and screening of bioactive components of tamarillos, collection and screening of tamarillo-related target proteins, collection and screening of disease-related target proteins and creation of target networks, creation of protein-protein interaction network (*PPI Network*) and enrichment analysis. Then, data analysis evaluates the characteristics of the preparation or product obtained from organoleptic and hedonic tests. The organoleptic test was analyzed based on observation of the preparation directly, while the acceptability evaluation was analyzed based on the questionnaire data obtained from respondents.

RESULTS AND DISCUSSION

Organoleptic test

An organoleptic test is a method of evaluating products in terms of the physical aspects of the product by relying on the sensory senses of 30 respondents. In this study, organoleptic tests conducted on tamarillo noodles included testing the taste, smell, colour, and texture of the noodles. The results of organoleptic tests can be observed in the following table III.

Tamarillo noodles are then calculated for Nutrition Facts using the Nutri Surveys and Calculations database to determine the nutritional content in the preparation. Each formulation obtained a total of 400 grams of noodles. The following is the nutritional content of tamarillo noodles (net: 100 g) and its comparison with instant noodles (net: 85 g) of certain brands that are well-known in the community (Table IV).

Based on the nutrition facts calculation result, the total energy for each package is 301.3 Kcal. These results are still classified as very safe for consumption by type 2 DM patients. According to the American Diabetes and American Diabetes Association, it is recommended that 50-60% of the calorie intake of type 2 DM patients be obtained from carbohydrates, 20-30% from fat, and 10-20% obtained from protein, where the maximum limit for calorie content is 1500 kcal/day (Cumayunaro et al., 2020). Thus, only one-fifth of the calories are allowed for type 2 DM patients in one package.

Hedonic Test

Hedonic tests are carried out to measure how much the public can accept tamarillo noodle products branded "Chypotes Noodle" products. The samples targeted by the hedonic test in this study were women and men with type 2 DM in the age range of 20 years to 55 years (20 people) and adolescents aged 20-25 years (10 people) with a ratio of Between genders, namely 1: 4 where the number of female respondents is more significant than men. The dominance of female respondents in this study is based on the scientific fact that women are more likely to experience type 2 DM than men. This fact comes up since women have a higher percentage of cholesterol than men, where fat in men ranges from 15-20% of body weight while women have 20-25%. Therefore, the factor of occurrence of diabetes mellitus in women is 3-7 times higher than in men (Rahmawati & Susilawati, 2021). Here are the results of the Chypotes Noodle hedonic test (Table V).

Based on the results of the hedonic test above, it is known that in the first question, 21 respondents chose option 4, and 9 respondents chose option 5, which showed that all respondents

liked the texture of Chypote noodles. In the second question, one respondent chose option 3 (neutral), 15 respondents chose option 4 (like), and 14 respondents chose option 5 (strongly like), indicating that most respondents like the color of the Chypotes Noodle. In question three, there was one respondent who chose option 3 (neutral), 13 respondents chose option 4 (like), and 16 respondents chose option 5 (very like), which indicates that Most respondents like the smell of Chypotes Noodle. In question four, option 4 (like) was chosen by 12 respondents, followed by option 5 (very like), chosen by 18 respondents, which showed most respondents liked the taste of Chypotes Noodle very much.

The last question obtained one respondent who chose option 3 (neutral), eight respondents chose option 4 (like), and 21 respondents chose option 5 (strongly like). The questionnaire results show that most respondents like and enjoy Chypotes noodle products, with a total percentage of 80-90% of respondents choosing the like and very like options. Thus, the post feedback from each question on this questionnaire shows that the chypotes noodle product can be well received and favoured by the community, especially people with DM Type 2.

Network Pharmacology Test

Collection and screening of bioactive components of Tamarillos

Based on the results of a literature study using the *Google Scholar* search engine with the keyword "*Cyphomandra betacea* compound", obtained the following results (Table VI).

Collection and screening of Tamarillo-related target proteins

Based on the collection and screening of target proteins from the *GeneCards* database with relevance values of ≥ 10.00 , 365 target proteins from various types of compounds were obtained (Table VII).

Collection and screening of disease-related target proteins and creation of target networks

From the 365 target proteins, 150 are specific and associated with type 2 diabetes mellitus (Non-insulin dependent) through DisGeNET. Then, the target network obtained from the visualization of *Cytoscape* v3.9.1 (Figure 2 and Figure 3).

The optimal target network (Figure 1) shows that six bioactive components of tamarillo have target proteins associated with type 2 DM disease. Thus, from 6 bioactive components (chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, 3-o-

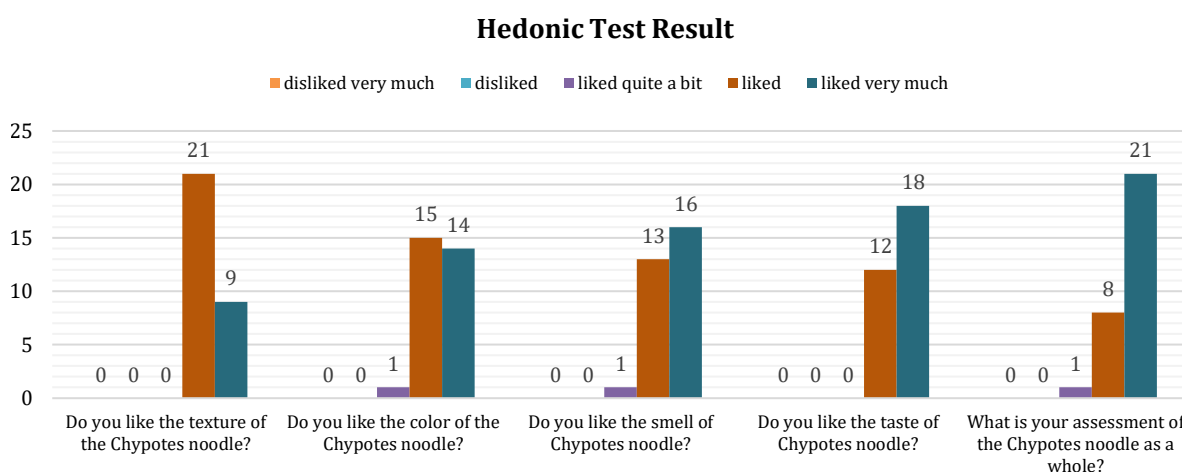


Figure 1. Hedonic Test Result

Table V. Hedonic Test Result

Question	1	2	3	4	5
Do you like the texture of the Chypotes noodles?	0 (0%)	0 (0%)	0 (0%)	21 (70%)	9 (30%)
Do you like the color of the Chypotes noodles?	0 (0%)	0 (0%)	1 (3%)	15 (50%)	14 (47%)
Do you like the smell of Chypotes noodles?	0 (0%)	0 (0%)	1 (3%)	13 (44%)	16 (53%)
Do you like the taste of Chypotes noodles?	0 (0%)	0 (0%)	0 (0%)	12 (40%)	18 (60%)
What is your assessment of the Chypotes noodle as a whole?	0 (0%)	0 (0%)	1 (3%)	8 (27%)	21 (70%)

Table VI. Bioactive components of Tamarillo

Compound Name	Molecular Type	PubChem CID	Book
keracyanin, pelargonidin 3-rutinoside, tulipanin, Delphinidin 3-O- α -l-rhamnosyl-(1-5,25)- β -d-glucoside	Anthocyanins	29231 44256626 5492231 443650	(Diep, Yoo, and Rush, 2022), (Elizalde-Romero et al., 2021), (Puspawati et al., 2018), (Reyes-García et al., 2021)
chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, 3-o-caffeoylquinic acid, quinic acid	hydroxycinnamic acids	1794427 689043 124202751 445858 1794427 6508	(Diep, Pook and Yoo, 2020), (Fredrika & Yanti, 2021)
β -carotene, β -cryptoxanthin, zeaxanthin	carotenoids	5280489 5281235 5280899	(Suárez-Montenegro et al., 2021), (Reyes-García et al., 2021), (Elizalde-Romero et al., 2021)
Kaempferol-3-rutinoside, kaempferol 8-C- β -d-galactoside, catechins, epicatechin	Flavonoids	5318767 14345562 163184559	(Diep, Pook and Yoo, 2020), (Diep et al., 2021), (Diep, Yoo and Rush, 2022), (Puspawati et al., 2018), (Fredrika and Yanti, 2021)
Gallic, Ellagic	hydroxybenzoic acids	370 5281855	(T. Diep et al., 2020) (Elizalde-Romero et al., 2021) (Diep et al., 2021) (T. T. Diep et al., 2022) (Pook et al., 2022), (T. T. Diep et al., 2021)

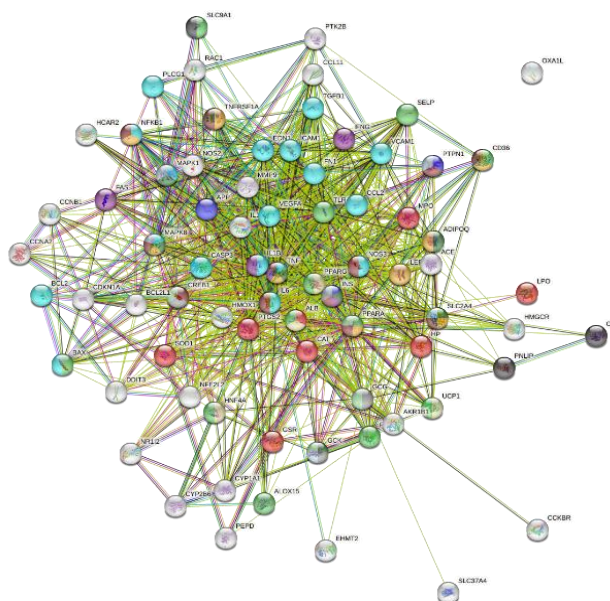


Figure 4. Interaction network of 150 core proteins from the *STRING* database (75 nodes, 988 edges, PPI enrichment p-value: < 1.0e-16)

Table VIII. Result of the KEGG gene interaction analysis of Tamarillo

Pathway	Description	Count in network	Strength	False Discovery Rate	Gene Ontology
Hsa04933	AGE-RAGE signaling pathway in diabetic complications	18 of 98	1.68	4.70E-22	Insulin receptor binding (GO:0005158)
HSA04930	Type II diabetes mellitus	7 of 46	1.6	8.70E-09	Antioxidant activity (GO:0016209)
HSA04920	Adipocytokine signaling pathway	9 of 69	1.53	2.01e-10	Fatty acid binding (GO:0005504)
HSA04940	Type I diabetes mellitus	5 of 39	1.52	3.20E-06	Lipid binding (GO:0008289)
HSA04931	Insulin resistance	12 of 107	1.47	6.31e-13	
HSA04911	Insulin secretion	4 of 82	1.1	0.00099	
HSA04910	Insulin signaling pathway	6 of 133	1.07	6.10E-05	
HSA04922	Glucagon Signaling Pathway	4 of 101	1.01	0.0020	

target genes for six bioactive components, namely *mitogen-activated protein kinase 1* (MAPK1), *Nitric oxide synthase 3* (NOS3), *Mitochondrial inner membrane protein OXA1L* (OXA1L), and *Myeloperoxidase* (MPO).

Creation of protein-protein interaction network (PPI Network) and enrichment analysis

This network pharmacology study revealed 75 target proteins associated with type 2 DM that are key targets, where they lock onto each other and detect each other (Figure 2). Tamarillo contains multicomponent multitarget work

through various mechanisms of action. Through pharmacological studies of this network, the mechanism of action of tamarillo can be described at the molecular level more comprehensively from upstream to downstream in the signaling pathway.

Based on the enrichment analysis of the mechanism of action of potential tamarillo against type 2 DM. The results of the analysis of KEGG identified target genes. The most associated target genes in the data are mitogen-activated protein kinase 1 (MAPK1), mitogen-activated protein kinase 8 (MAPK8), Tumor Necrosis Factor (TNF), Insulin (INS), Adiponectin (ADIPOQ), Solute Carrier Family 2 Member 4 (SLC2A4).

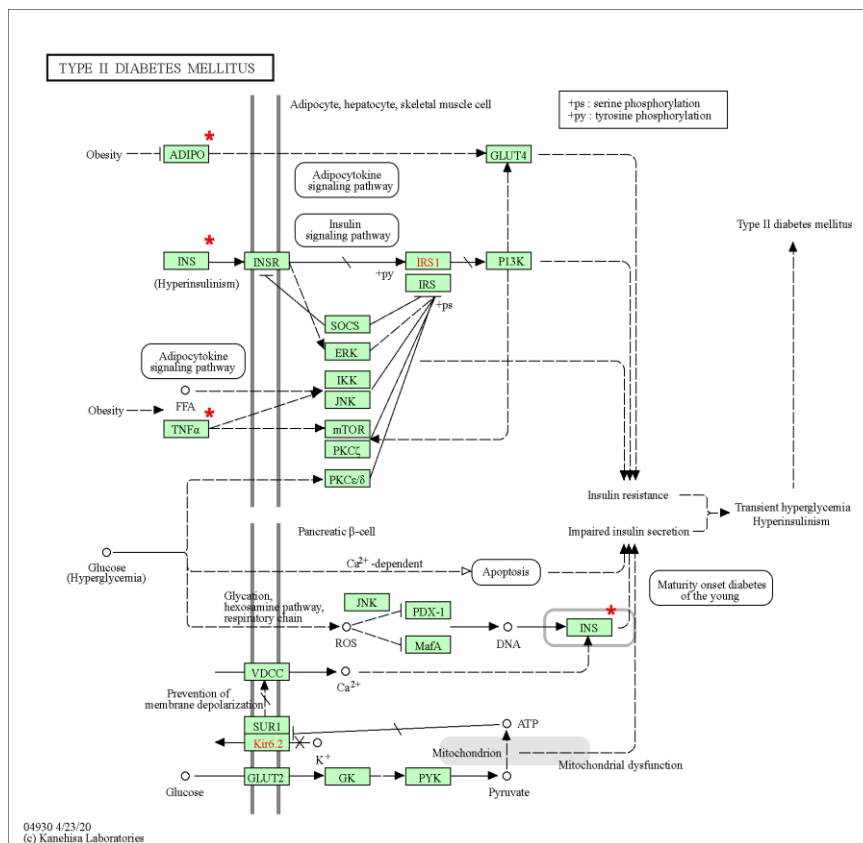


Figure 5. Type II Diabetes Mellitus signal line (KEGG:04930)

This study shows that tamarillo affects the biological processes and signaling pathways of type 2 DM against *Adiponectin* (ADIPOQ) (GO: 0389814), *Tumor Necrosis Factor* (TNF) (GO: 0398698), and *insulin* (INS) (GO: 0380432). *Adiponectin* (ADIPOQ) is adipokine produced and secreted by adipocytes. ADIPOQ is a vital adipokine that controls fat metabolism and insulin sensitivity, with direct anti-diabetic, anti-atherogenic, and anti-inflammatory activities. It stimulates AMPK phosphorylation and activation in the liver and the skeletal muscle, enhancing glucose utilization and fatty-acid combustion (Nguyen, 2017). Low serum ADIPOQ concentrations are the cause of diabetes. In individuals with type 2 diabetes, ADIPOQ levels in the blood tend to be low so that insulin resistance increases (Howlader et al., 2021).

Tumour necrosis factor alpha (TNF- α) is a cytokine released by adipocytes and inflammatory cells in response to chronic inflammation, namely DM type 2. TNF- α is the first proinflammatory cytokine to have involvement in the pathogenesis of insulin resistance. TNF- α reduces expression in insulin-regulated glucose transporter type 4 (GLUT4) located primarily in adiposity, bone, and

heart muscle. In addition, TNF- α , by inducing serine phosphorylation of insulin receptor substrate-1, acts as an inhibitor of peripheral insulin action causing insulin resistance (Alzamil, 2020). In individuals with type 2 diabetes, TNF levels in the blood tend to be high, causing chronic inflammation and disrupting insulin function.

Insulin (INS) lowers blood glucose concentrations, increases cell permeability to monosaccharides, amino acids, and fatty acids, and accelerates liver glycolysis, pentose phosphate cycle, and glycogen synthesis. *Insulin* is a hormone produced by beta cells in the pancreas and functions to regulate glucose metabolism. In individuals with type 2 diabetes mellitus, the body loses the ability to respond effectively to insulin, so glucose cannot eventually be stored in the cells and adequately builds up in the blood. This condition is called insulin resistance (Tran et al., 2020).

Overall, an imbalance between INS, ADIPOQ, and TNF can lead to insulin resistance and inflammation, which are key characteristics of type 2 diabetes. Thus, tamarillo compounds upregulate these three proteins to increase insulin sensitivity and prevent inflammation.

CONCLUSION

Tamarillo noodles (Chypotes Noodle) organoleptically have a chewy texture, a distinctive noodle smell, a yellow color, and a slightly sour tasteless typical of Tamarillo. Based on the results of the hedonic test, 30 respondents chose the like and very like option in filling out the questionnaire with a percentage of 80-90% which proves that this product is accepted and liked by the public. Based on *the Network Pharmacology* of Tamarillo shows that 150 of the 365 target proteins of Tamarillo are involved in the biological processes and signaling pathways of type 2 diabetes mellitus, with 75 target proteins locking and interacting. Among the compound molecules in Tamarillo, six bioactive components from the hydroxycinnamic acids group have activity in type 2 DM. These compounds affect the biological processes and signaling pathways of type 2 DM against ADIPOQ, TNF, and INS. Therefore, Tamarillo can potentially be used as an alternative food product in the form of noodles for type 2 DM treatment.

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