JKKI
SCIENTIA EST BASIC VITAE

Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage: https://journal.uii.ac.id/JKKI

Target protein prediction of Indonesian *jamu kunyit asam* (*Curcuma-tamarind*) for dysmenorrhea pain reliever: A network analysis approach

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Original Article

ARTICLE INFO

Keywords:
Curcuma longa,
Dysmenorrhea,
Jamu,
Network pharmacology,
Tamarindus indica

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DOI: 10.20885/JKKI.Vol12.Iss3.art7

History:
Received: May 10, 2021
Accepted: December 16, 2021
Online: December 31, 2021

ABSTRACT

Background: Dysmenorrhea is a monthly problem for reproductive-age women before or during menstruation. Dynamic changes of prostaglandins (PGs) and progesterone in the late reproduction cycle regulating signal pathways of PGE2 and PGF2 can contribute to menstrual cramps and other dysmenorrhea symptoms. Curcuma longa and Tamarindus indica (CT) are traditional medicines more preferred by Indonesian women to overcome menstrual pain than painkiller drugs.

Objective: This study aims to observe potentially active compounds and detailed mechanism of Curcuma longa and Tamarindus indica (CT) as a pain reliever.

Methods: Bioactive compounds in the CT were collected from two databases and then screened by bioavailability and drug-likeness parameter by utilizing SwissADME software. The target proteins and genes associated with dysmenorrhea were retrieved from HitPick and GeneCard database. The possibility of how CT healed dysmenorrhea was predicted by protein-protein interaction (PPI) using STRING Webserver and was visualized by Cytoscape v.3.7.0 and REVIGO.

Results: Totally, 147 active compounds were obtained from C. longa and 212 active compounds from T. indica. Respectively, 36 and 66 compounds were obtained from C. longa and T. indica by the ADME screening. Finally, 20 and 22 target proteins were identified in both herbs. Then, an overlap analysis of this study showed that four target proteins had strong interaction with pain-related dysmenorrhea

Conclusion: This study found possible target proteins of the CT to relieve dysmenorrhea. The target proteins included HSD17B1, ALOX5, GSTM1, and ESR2 genes. Further, these findings are needed to be validated by using in vitro and in vivo approaches.

Latar Belakang: *Dismenorea merupakan permasalahan yang dialami oleh wanita usia reproduksi sebelum dan/atau setelah menstruasi. Dinamika perubahan pada prostaglandin (PG) dan progesteron di akhir siklus reproduksi meregulasi jalur sinyal PGE2 dan PGF2 menyebabkan kram menstruasi serta*

gejala dismenorea lainnya. Curcuma longa dan Tamarindus indica (CT) adalah obat tradisional pilihan utama wanita Indonesia yang mengalami nyeri menstruasi dibandingkan obat penghilang rasa sakit

Tujuan: *Tujuan studi ini adalah untuk mengetahui senyawa yang berpotensi aktif dan mengungkap mekanisme CT sebagai herbal pereda rasa nyeri*

Metode: *Senyawa aktif pada CT dikoleksi dari dua database, kemudian dilakukan penapisan berdasarkan parameter bioavailability dan drug-likeness menggunakan SwissADME. Target protein dan gen yang berkaitan dengan dismenorea, masing-masing didapatkan dari database HitPick dan Genecard. Kemungkinan terkait dengan mekanisme CT mengobati dismenorea diprediksi menggunakan pendekatan interaksi protein dan protein (PPI) dengan website STRING dan divisualisasikan dengan Cytoscape v.3.7.0 dan REVIGO.*

Hasil: *Secara total, terdapat 147 senyawa aktif yang didapatkan dari C. longa dan 212 dari T. indica. Secara berturut-turut, 36 dan 66 senyawa aktif didapatkan dari C. longa dan T. indica dari hasil penapisan ADME. Pada akhirnya, 20 dan 22 target protein potensial didapatkan dari kedua tanaman tersebut. Analisis pencocokan menghasilkan empat protein yang memiliki integrasi kuat dengan nyeri akibat dismenorea.*

Kesimpulan: *Data kami menyediakan protein yang mungkin di target oleh jamu CT untuk meredakan nyeri menstruasi. Target tersebut antara lain HSD17B1, ALOX5, GSTM1, dan ESR2 gen. Lebih lanjut, temuan ini perlu di validasi melalui pendekatan in vitro dan in vivo.*

INTRODUCTION

Dysmenorrhea is a painful and cramp condition in the abdomen part, especially in the lower area, usually occurring before or during menstruation in a woman. This condition is frequently followed by other symptoms such as headaches, nausea, sweating or diarrhea.[1] There are two types of dysmenorrhea condition, primary and secondary dysmenorrhea. Primary dysmenorrhea refers to the pain or cramp without pathology, while secondary dysmenorrhea is associated with pathology such as endometriosis.[2] Cross-sectional studies have found that 2-29% of 16-91% of reproductive-age women experience severe pain during menstruation. This condition is closely related to the stress with varied odds ratios between 1 to 4 (modest to moderate).[1] A study also mentions that family history can be related to dysmenorrhea such as endometriosis and genetic factors. Besides, alcohol, stress and physical activity are also related to the severeness of dysmenorrhea.[3] Another study states that dysmenorrhea symptoms can intervene daily activities.[4] Even though every woman does not experience the dysmenorrhea symptoms, awareness and knowledge about dysmenorrhea are needed to be spread.

Primary dysmenorrhea is the most common symptom experienced by a woman. It is started by the imbalance of prostaglandins (PGs) concentration from endometrium. To be highlighted, the hypersecretion of prostaglandins and increased uterine contractility are responsible for any pain associated with dysmenorrhea.[5] Its general symptom is the manifestation of PGs influx through a systemic circulation. Arachidonic acid synthesis and cyclooxygenase are expressed when the progesterone concentration has been reduced in the late phase. Generally, the PG levels are significantly secreted during a menstrual phase. This leads to cascade signalling of prostaglandin E2 (PGE2) and prostaglandin F(2a) or PGF2, which causes menstrual pain.[2] The PGF2 is identified as a key regulator of menstrual cramps, leading the uterine vasoconstriction and myometrium contraction, while PGE2 acts in both relaxation and contraction. During menstruation, the PG expression can produce pain, inflammation, changes of body temperature and circadian clock.[6]

Indonesian women routinely consume a traditional herbal medicine (called jamu) consisting of Curcuma longa and Tamarindus indica (CT) as a treatment to soothe the menstrual cramp or primary dysmenorrhea. Several studies on women with different statistical analysis methods indicated the CT jamu consumption positively reduced pain levels of menstrual cramp. A scientific reason mainly

mentioned that phenolic composition in the CT acts as an inhibitor of cyclooxygenase (COX), contributing to inflammation.[7,9] A study also stated that the women more preferred jamu or herbal consumption than painkillers such as Ibuprofen or mefenamic due to its low side effects.[7] This is also supported by the government campaign movement, especially by the Ministry of Health to utilize medicinal plants (or called tanaman obat keluarga (TOGA)). An industrial-scale of CT (called *jamu kunyit asam*) has also been produced by a pharmaceutical company in Indonesia.

This current study addresses wider issues associated with complex interaction between active compounds in the CT and its target proteins, enriched with gene annotation including molecular function, biological process, cellular component, KEGG pathway, and protein-protein interaction associated with pain-related genes. Therefore, this study observes mechanism of action underlying the CT consumption for dysmenorrhea and points out several novel proteins contributing to menstrual pain.

METHODS

To obtain the active compounds from both *Curcuma longa* and *Tamarindus indica*, this study utilized phytochemical databases from Dr Duke Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/phytochem/search) and KNApSack (http://www.Knapsack family.com/KNApSAcK/).[10] The compound ID and canonical SMILE data were collected (Supplementary data 1).

ADME analysis and target protein analysis

The ability of each compound from both herbs were analysed by SwissADME11 (http://www.swissadme.ch/), generating properties of active compound such as MW, formula, solubility, GI absorption, BBB permeability, and bioavailability. Compounds with bioavailability >0.5, BBB permeability, high GI absorption, and solubility rated from moderately soluble to very soluble were chosen as the first stage sample. The target proteins of all the chosen compounds were identified by HitPick software.[12] At the same time, the genes associated with dysmenorrhea were obtained from GeneCard Database. Visualization of the Venn diagram was generated by using online Venn diagram generator by inputting the list of proteins (http://bioinformatics.psb.ugent.be/ webtools/Venn/).

Network construction

The interaction between protein or protein-protein interaction (PPI) was built by the STRING webserver. The protein interaction was then clustered into four clusters by k-means to classify functions of each protein. Its visualization was conducted by using Cytoscape v.3.7.0 to determine the target proteins of each herb.[13]

Enrichment analysis

The STRING networking automatically generated enrichment analyses of this study, including biological process, molecular function, cellular component, and KEGG pathway which were related to each protein target.[14] The data were then visualized by using the REVIGO software in treemaps graph (http://revigo.irb.hr/).[15]

RESULTS

The active compounds of C. longa and T. indica

This study respectively found 73 and 74 active compounds of C. longa from Dr. Duke Phytochemical database and KNApSack, and 101 and 11 active compounds of T. indica were respectively obtanined from Dr. Duke Phytochemical database and KNApSack. The average of chemical properties of herbs pair was showed in Table 1. In general, the average of MW and heavy atoms of active compounds from the herb pair indicated a close similarity value. 147 and 112 active compounds from C. longa and T. indica were used for further analysis.

Table 1. The average of chemical properties of active compound curcuma and tamarind herb pair

Herb	MW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3	#Rotatable bonds	#H-bond acceptors	#H-bond donors
C. longa	219.56	15.69	2.38	0.58	3.03	1.83	0.91
T. indica	198.65	13.90	2.68	0.54	3.93	3.42	2.05

ADME properties of CT active compounds and target proteins

The druglike-ness of each compound was then determined by the ADME prediction analysis. From 147 active compounds in C. longa, only 36 compounds had moderate to very soluble properties, high GI absorption, BBB permeant, and bioavailability score >0.5. Meanwhile, 66 compounds were successfully filtered from T. indica based on the same ADME qualification (Supplementary data 2a and 2b). Those chosen compounds were then explored further based on their target proteins. Based on the target protein prediction, C. longa had 20 target proteins including GSTM1, APP, CHRM4, PTGR1, HCAR2, FAAH, SLCO2B1, GLTP, TYR, CHRM1, SLC22A5, PRKACA, UQCR11, HSD17B1, PRSS3, F2, LCN9, CTRC, CA5A, and MAOB. Then, the T. indica had 22 target proteins including GSTM1, FAAH, SLC22A11, HTR2B, CRABP2, SLC22A8, HCAR2, FNTA, ESR2, TAAR1, CA2, SLC22A6, SLC22A5, FKBP4, RABGGTB, PRSS1, BCHE, ALOX5, MAOB, FKBP1C, CHRM1, and CES1.

CT compounds and target network

From 42 target proteins of the herb pair, the networking analysis pointed out some new possible networks, implicating new protein-related target of the herbs. After clustering based on k-means, the networks were divided into four clusters, implicating groups of proteins related to specific diseases. The proteins in red, yellow, green and blue clusters exemplified specific functions.

Interestingly, the KEGG enrichment in each cluster formed by the STRING analysis indicated terms related to metabolic and complex diseases, such as Parkinson's and Alzheimer's disease in the red and blue cluster. The yellow cluster showed complement and coagulation cascades and platelet activation. In comparison, the green cluster demonstrated an interaction related to the neuron, influenza A and secretion of the pancreatic organ (Figure 2).

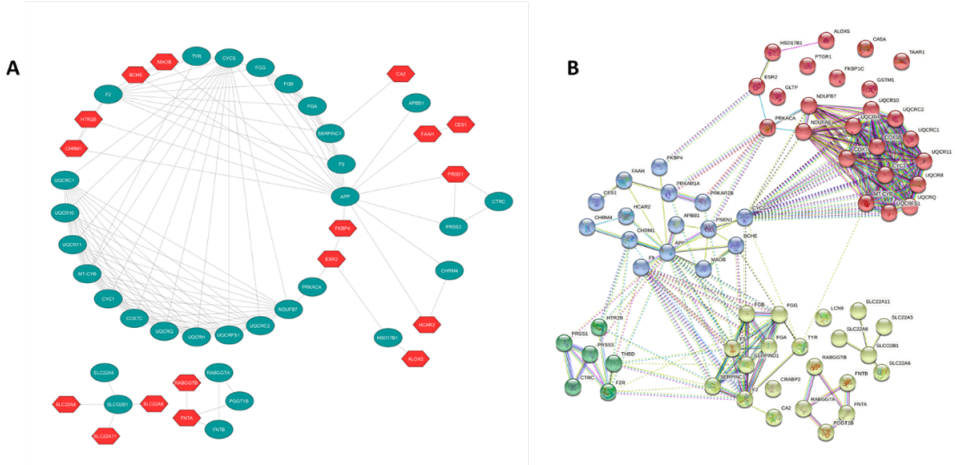


Figure 1. Networking analysis generated by using Cytoscape software. The orange triangle represents T. indica target, the dark green circle represents C. longa target (A), and network clustering is based on k-means (B)

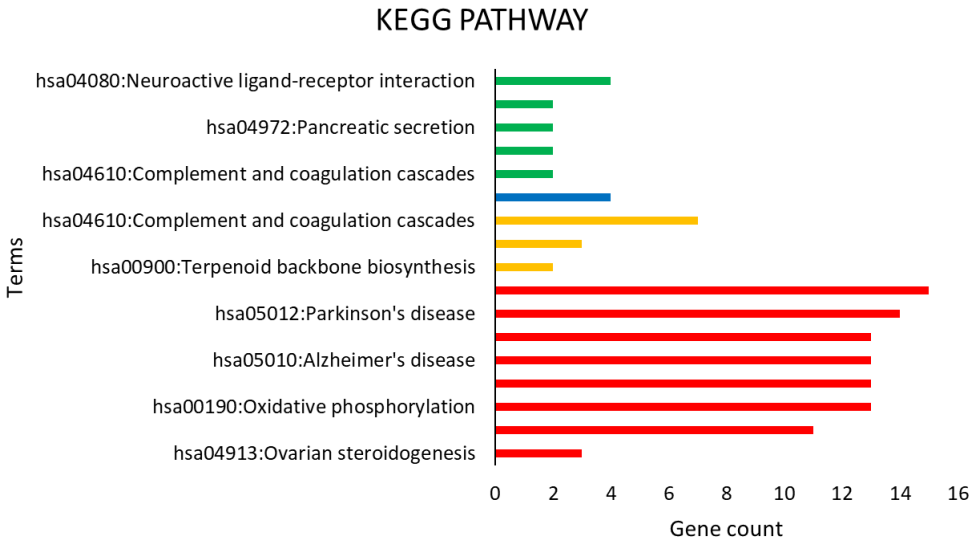
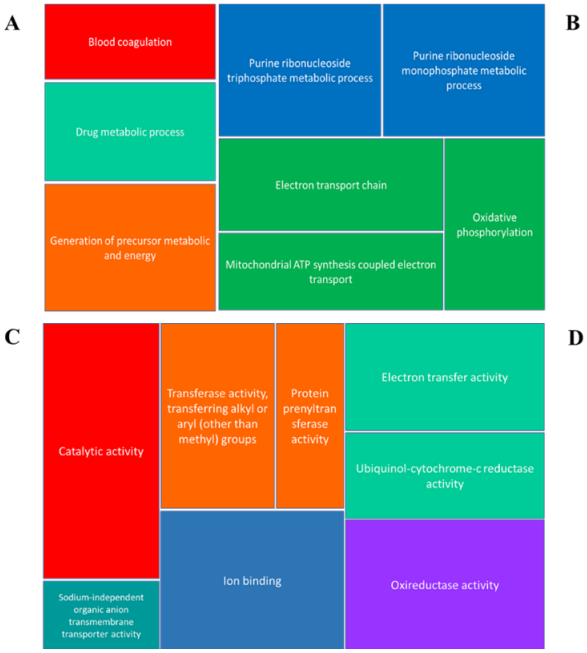


Figure 2. KEGG pathways of protein clusters in the enrichment analysis. The bar colours represent each cluster generated in network clustering

Enrichment analysis of CT target network

To explore the molecular function, process and component of 42 target proteins of active compounds of the herbs, the enrichment analysis of biological process demonstrated some terms related to oxidative phosphorylation, mitochondrial transport and synthesis, electron transport chain, generator of precursor metabolites energy and oxidation-reduction process. The enrichment function mainly pointed out terms related to electron transfer activity, ubiquinol cytochrome-c-reductase activity and oxy-reductase activity. Interestingly, the KEGG enrichment revealed terms related to complex diseases, such as Alzheimer's and Parkinson's, with high FDR (Figure 3).



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KEGG	ID	Term description	False Discovery Rate (FDR)
1	hsa05010	Alzheimer's disease	9.36E-20
2	hsa05012	Parkinson's disease	5.35E-18
3	hsa04932	Non-alcoholic fatty liver disease (NAFLD)	2.69E-16
4	hsa00190	Oxidative phosphorylation	1.31E-15
5	hsa04260	Cardiac muscle contraction	3.03E-15
6	hsa05016	Huntington's disease	4.93E-15
7	hsa04714	Thermogenesis	4.31E-14
8	hsa04610	Complement and coagulation cascades	5.15E-12
9	hsa01100	Metabolic pathways	4.53E-08
10	hsa04080	Neuroactive ligand-receptor interaction	5.39E-05

Figure 3. Enrichment of biological process (BP) (A), cellular component (CC) (B), molecular function (MF) (C), and KEGG pathways (D)

Overlap analysis between CT compound targets and pain associated with dysmenorrhea

Next, the target proteins of the CT were overlapped to specify the targets of the CT. Six proteins were intersected as the targets of the CT, including GSTM1, FAAH, HCAR2, SLC22A5, MAOB, CHRM1 (Figure 4a). The KEGG enrichment analysis of 6 proteins was performed to explore their potential. As shown in Figure 4b, the potential pathways representing the mechanism of action of herb pair included drug metabolism, cAMP signalling pathways and phenylalanine metabolism.

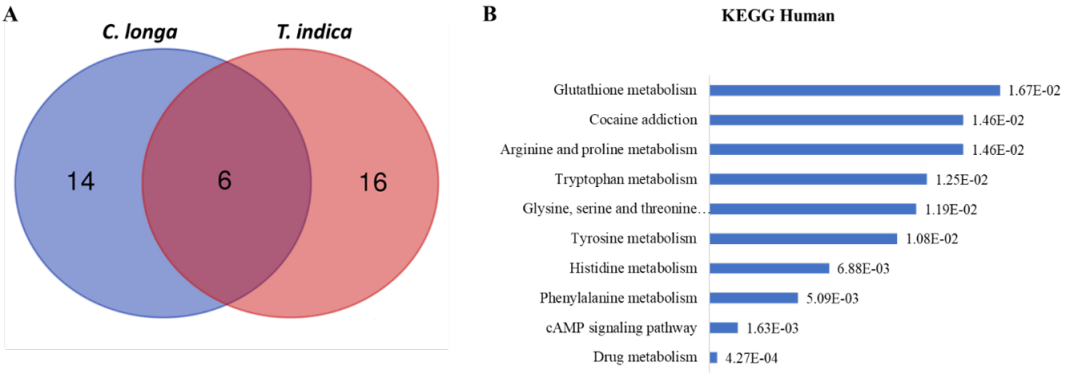

Figure 4. Venn diagram for the overlap analysis of target proteins of C. longa and T. indica (a) and KEGG enrichment of six overlap genes from herb pair (b)

To identify the molecular mechanism of the CT to relieve the dysmenorrhea pain, the target proteins of the CT were overlapped with target proteins obtained from the database. To minimize the bias, the researchers removed redundant proteins found in the CT targets. From 36 protein targets of the CT and 239 proteins related to the dysmenorrhea pain, four proteins,including HSD17B1, ALOX5, GSTM1 and ESR2 were identified overlapped (Figure 5). Referring back to the roots, HSD17B1 was the initial target protein from D-Champene and Guaiacol in C. longa. In contrast, ALOX5 targeted Alpha terpineol, GSTM1 from Cinnamaldehyde and D-Arabinose, and ESR2 was the target of Behenic acid identified in T. indica.

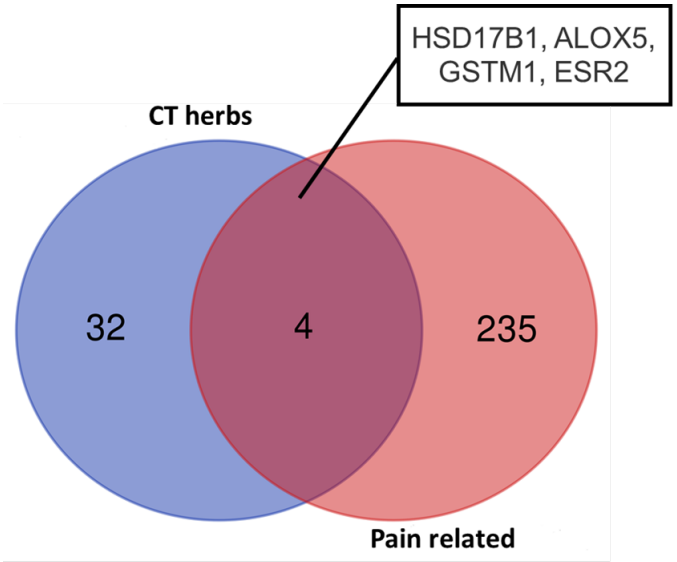

Figure 5. Overlap analysis between CT target genes and pain-related dysmenorrhea

DISCUSSION

This study performed several steps of screening from the active compounds identified from the phytochemical databases. The first level of screening was related to the adsorption, distribution, metabolism and excretion (ADME) parameters; one of them was solubility level with scales from moderate to very soluble. The drugs were classified into four classes, including class I for high solubility, class II for low solubility, class III for low solubility and high permeability, and class IV for low solubility and permeabilty.16 The solubility parameter was based on the strength of the highest dose to release the insulin instantly. Generally, the highly soluble drugs dissolve in 250 mL of aqueous media with a pH range from 1 to [7.5.] The number 250 mL is derived from protocol bioequivalence study of a drug administration to a fasting human with a glass of water.[17] The importance of solubility parameters are related to the formulation and concentration of drug to be circulated in the systemic body. Besides, the absorption of a drug is highly correlated to the solubility so that performance of a drug easily achieved its targets.16 This is also related to the high GI absorption parameters because the oral route of a drug will be ended up in the GI tract and absorbed by passive diffusion or active transport. The absorption rate depends on the concentration, MW, size, lipid solubility, blood flow, surface area and permeability score. In addition, the pH plays important roles according to the pH partition hypothesis.[18] The third filter parameter applied in this study was blood-brain barrier (BBB) permeant. As BBB determine central nervous systems from the peripheral tissue, the balance of material, nutrient and cell transfer between the brain to blood and vice versa should be maintained.[19] The BBB system forbids inflammatory mediators such as cytokines, antibodies that lead to neurotransmission impairment. Also, with the advancement of neuroimaging methods, a growing number of studies have confirmed that primary dysmenorrhea is linked to structural and functional brain changes. During painful menstruation and pain-free periovulatory phase, brain functional abnormalities are detected in default mode networks, including ventromedial prefrontal cortex, ACC, PCC, praecuneus, inferior parietal cortex, inferior temporal cortex, hippocampus, and thalamus. In addition, anterior insula (AI) was discovered, as well as hypoconnectivity.[20] Therefore, the CT treatment should be able to permeate through BBB systems to inhibit the cascade signalling. The last parameter in the ADME that the researchers applied is a bioavailability score of more than 0.5. The drug bioavailability defines the ability of drugs to reach systemic circulation. The bioavailability does not influence the adsorption; instead, it is affected by factors that regulated the adsorption, such as lipophilicity, size, polarity, solubility, flexibility, and saturation.[21]

After screening using several parameters by the ADME, target proteins of selected active compounds was then predicted. The prediction identified 42 proteins from the CT and generated a network, as shown in Figure 1. Next, the researchers classified them into four clusters based on k-means. The k-means divided the network operations into clusters based on similarity score and distinctive value. Nevertheless, the quality of the clusters generated based on the initial target roles, which sometimes could be poor due to random selections; for example, when an outlier data point was chosen as a starter.[22] Interestingly, the KEGG pathways generated from the STITCH database in the green cluster indicated the terms related to neuroactive ligand-receptor interaction (hsa04080), involving PGE2 and PGF2 alpha (red box, Figure 6). The involvement of PGE2 and PGF2 alpha was already mentioned in several studies, leading to the target and management therapy used by the non-steroidal anti-inflammatory drug (NSAID) to overcome dysmenorrhea.[23] In the women with primary dysmenorrhea, PGE2 and PGF2 alpha level were elevated compared to healthy controls.[24] This expression pattern was used as a strategy to inhibit COX2 as the upstream PGs using NSAIDs as a therapy. It is known that NSAIDs bind to COX1 and COX2, inhibiting the synthesis of prostaglandin.[23]

CONCLUSION

The study revealed that the ultimate target genes of CT consumption were involved in the primary and secondary dysmenorrhea, which still need further validation and confirmation about types of target interaction. By targeting HSD17B1, ALOX5, GSTM1 and ESR2 genes, the CT may help dysmenorrhea patients relieve or attenuate their pain.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENT

The authors thank to Ms. Anggia NR, who facilitated to use Cytoscape features.

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