Prediction of the potency of active compounds in pasak bumi root as the treatment for prostate cancer through phosphatase and tensin homolog (PTEN) pathway

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Research Article

Prediction of the potency of active compounds in pasak bumi root as the treatment for prostate cancer through phosphatase and tensin homolog (PTEN) pathway

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ABSTRACT

Background. Prostate cancer is one of the most commonly reported health problems in males. Prostate cancer is also the second most commonly diagnosed cancer worldwide. Currently, the incidence of prostate cancer in Indonesia is the third highest after lung and colorectal cancers. Pasak Bumi (E. longifolia jack) , from its root to its seed, are commonly used as traditional drug in that contain various active compounds. pasak bumi might have a potential as cancer suppression treatment.

Aim. To assess the potency of active compounds in pasak bumi root as prostate cancer treatment in prostate adenocarcinoma PC-3 cells through PTEN pathway.

Methods. Prediction Of Potency. The compounds in pasak bumi were searched through literature review and the SMILES (simplified molecular-input line-entry system) in the PubChem database. The potency of the compounds was analyzed with WAY2DRUG PASS prediction as anticancer.

Prediction of target. All the targets of herbal compounds were analyzed with SWISS Target Prediction in Homo sapiens. In SWISS Target, input compound was compared to other compounds in the database that have been proven to have an activity on the target protein. The more alike, the higher the similarity score.

Prediction of pathway. The target predicted in stage 2 was analyzed for its interaction with target protein PTEN using the webserver STRING DB Version 11.0 in Homo sapiens model and a high confidence of 0.7 (the value that illustrate the literature supporting the results). The STITCH results provided a prediction of the pathway visualized with different colours with different meanings. Prediction score was obtained through STRING algorithm and synthesized from published study results.

Results: Based on PASS analysis, the derivative compounds in pasak bumi, including eurycomanone, have the activity as antineoplastic in prostate (Pa > 0.7) and apoptosis agonist (Pa > 0.7). The results of SWISS Target show that the compounds in pasak bumi may interact with KDR, NFκB1, and bcl2. Meanwhile, the results in PASS server show that they may interact with p53. Furthermore, they interacted with the target protein, namely, PTEN.

Conclusion: Pasak bumi can become a candidate for prostate cancer, because it increases the expression of p53. p53 has a role in DNA damage, and affects the expression of PTEN that facilitates the elimination of cancer.

Keywords: Pasak bumi root, Prostate cancer PETN

INTRODUCTION

Prostate cancer is one of the most commonly reported health problems in males. Prostate cancer is also the second most commonly diagnosed cancer worldwide.[1] Currently, the incidence of prostate cancer in Indonesia is the 3rd highest after lung and colorectal cancers.[2] Prostate cancer is the most frequently diagnosed non-skin cancer and the second cause of death in the United States of America.[3] Several studies showed a 40% risk of latent prostate cancer among 50 years-old males, 9.5% of these are symptomatic and 2.9% of them lead to death.[4] The incidence of prostate cancer in under 30 years old increases from 5% to 59% in males over 79 years old. Globally the incidence of prostate cancer increases significantly, particularly in Asia, Northern Europe, and Western Europe .[5]

A high quality of life is associated with high incidence and mortality rates of prostate cancer. Metastatic prostate cancer, as well as its resistance to chemotherapy result in a high mortality rate. Delayed diagnosis and increased chemoresistance lead to a 5-year survival rate of less than 50%. Therefore, the development of effective and non-toxic drugs is critical for prostate cancer patients.[6]

Genetics and epigenetics have important roles in the carcinogenesis of prostate cancer. Mutated genes in prostate cancer are p27, p53, PTEN, bcl-2, NFκB, and KDR.[7] One of the tumor suppressors which expression is decreased in prostate cancer is p27 that has an important role in controlling the cell development from G1 phase to S by binding and inhibiting cyclin E-CDK2 complex which inactivation is affected by the loss of PTEN protein.[8] PTEN is a tumor suppressor gene that induces cellular apoptosis through its modulation of PI3K/Akt. One important pathway in prostate cancer is phosphoinositide 3-kinase (PI3K). It is assumed that this pathway has a role in 30-50% prostate cancer.[9] The inactivation of bcl-2 in PI3K/Akt pathway in prostate cancer cell may increase cell apoptotic process.[10]

Eurycome longifolia Jack or pasak bumi is one of the plants widely used by populations in South-eastern Asia as traditional drug.[1] All parts of pasak bumi, from its root to its seed, are commonly used as traditional drug in that contain various active compounds.[11] Pasak bumi root has the following active compounds: eurycomanone, quassinoids, coumarins, glycosides, phenolic compounds, tannin, eurycomanone, eurycomanol, eurycomalactone, canthine-6-one alkaloid, 9-hydroxy canthin-6-one, 15β-dihydroxyklaneanone, and triterpenes.[12-13]The active compounds in pasak bumi root have anticancer effect towards skin, breast, lung, fibrosarcoma colorectal, and ovarian cancers.[14] The active compounds in pasak bumi root may induce apoptosis in breast cancer (MCF7) through a decreased expression of bcl-2.[15] In a study by Nuraini, methanol extract of pasak bumi administered to breast cancer cells led to the inhibitor activation of COX-2 expression, a decrease in bcl-2 expression, an increase in p21 and p53 expression,[16] which result in the conclusion that pasak bumi might have a potential as cancer suppression treatment.

Aim of the study: To assess the potency of active compounds in pasak bumi root as prostate cancer treatment in prostate adenocarcinoma PC-3 cells through PTEN pathway.

Methods

Prediction of potency

The compounds in pasak bumi were searched through literature review and the SMILES (simplified molecular-input line-entry system) in the PubChem database. The potency of the compounds was analyzed with WAY2DRUG PASS prediction (http://pharmaexpert.ru/PASSonline/index.php) as anticancer.

Prediction of target

All the targets of herbal compounds were analyzed with SWISS Target Prediction (http://www.swisstargetprediction.ch/index.php) in Homo sapiens. In SWISS Target, input compound was compared to other compounds in the database that have been proven to have an activity on the target protein. The more alike, the higher the similarity score (the maximal score is 1).

Prediction of pathway

The target predicted in stage 2 was analyzed for its interaction with target protein PTEN using the webserver STRING DB Version 11.0 (https://string-db.org/) in Homo sapiens model and a high confidence of 0.7 (the value that illustrate the literature supporting the results). The STITCH results provided a prediction of the pathway visualized with different colours with different meanings. Prediction score was obtained through STRING algorithm and synthesized from published study results.

Results

PASS server

The following are the results of Pa values for activities related to herbal protein as anticancer. The value of Pa (probability to be active) is a value describing the potency of a tested compound. The determination of this value was conducted by comparing the structure of herbal

compound input with the structure of the compound proven as anticancer and has a potency with a certain activity.

The Pa of more than 0.7 means that the compound is predicted to have a high potency, since it has a high similarity with the compound proven to have a certain activity. When the value of Pa is more than 0.3, but less than 0.7, the compound has a computed potency, but the similarity with a compound that has been proven to have a certain activity is low.

Table 1. Prediction of the potency of pasak bumi (Eurycoma longifolia) - Results from the PASS server analysis

Compound	Eurycomanone	9-Methoxycanthin-6-one	Canthin-6-one / canthinone
PubChem CID	433873	9881423	97176
Antineoplastic	0.979	0.47	0.36
Apoptosis agonist	0.872	0.293	
Transcription factor NF kappa B inhibitor	0.482		
Antimetastatic	0.473		
Prostate cancer treatment	0.143	0.185	
Caspase 8 stimulant	0.375	0.322	
Immunosuppressant	0.784		
Antineoplastic Enhancer			0.444
Antioxidant	0.224		
AR expression inhibitor	0.195		
Kallikrein 3 inhibitor			0.065
Prostate Disorder Treatment		0.208	0.192
TP53 expression enhancer	0.35	0.307	0.321

Based on the analysis, the derivative compounds in pasak bumi, including eurycomanone, have the activity as antineoplastic in prostate (Pa > 0.7) and apoptosis agonist (Pa > 0.7).

Prediction of target protein

Pasak bumi compounds were predicted to target proteins that have a role in progression, metastasis, cell cycle, and proliferation in prostate cancer. The results of SWISS Target show that the compounds in pasak bumi may interact with KDR, NFκB1, and bcl2. Meanwhile, the results in PASS server show that they may interact with p53. Furthermore, they interacted with the target protein, namely, PTEN (Figure 1).

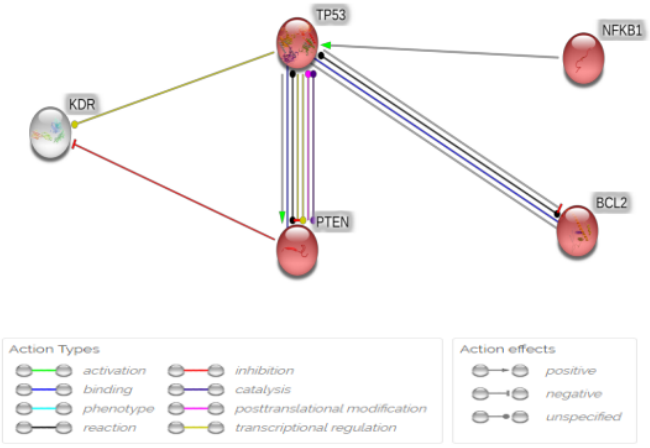

Fig.1:The interaction between target protein and PTEN. The red colour shows the proteins involved in prostate cancer that were recorded in the KEGG pathway.

DISCUSSION

Eurycoma longifolia Jack or usually known as pasak bumi is one of the plants that has been utilized by the populations in South-eastern Asia as traditional drug. Silalahi (2015) stated that all parts of pasak bumi may be used as a drug, from the root to the seed. The utilization of plants as drug is associated with bioactive compounds contained in it. Some plants produce different bioactive compounds in different organs.[11,17]

Pasak bumi root contains the following active compounds: eurycomanone, quassinoids, coumarins, glycosides, phenolic compounds, 12nin, eurycomanone, eurycomanol, eurycomalactone, canthine-6-one alkaloid, 9-hydroxy canthin-6-one, 14, 15β-dihydroxyklaneanone, and triterpenes.[12,13] Pasak bumi has antiosteoporotic, antioxidant, antiinflammatory, antiproliferative, and anticancer effects.[18] The results from Nurhanan's study (2005) showed that methanol extract of pasak bumi root had cytotoxic effect in breast and ovarian cancers.[19] According to Tong (2015), the active compound quassinoids in pasak bumi root have cytotoxic effect in 2rostate cancer and may inhibit the proliferation of cancer cells.[20] In this study, the active compounds in pasak bumi, namely eurycomanone and 9-methoxycanthin-6-one canthinone, has the activity as anticancer in prostate, one of the mechanisms is through NFκB inhibitor, apoptosis agonist, TP53 expression enhancer (which has a role in DNA damage), and kallikrein 3 inhibitor (inhibitor of prostate specific antigen/PSA, in prostate cancer with upregulated PSA).

According to Damodaran (2016), the activity of bcl-2 has an important role in apoptosis of prostate cancer cells. Generally, bcl-2 may initiate cell death in several mechanisms, caspase-independent effect on mitochondria, regulation of CED-4 and pro-apoptotic proteins (Bax, Bad, Bak, Bcl-xs, Bid, Bik, and Hrk) that may accelerate the cell death. bcl-2 expression is regulated by p53 protein and NFκB. Induction of bcl-2 protein mediated by NFκB will reduce the ratio of Bax that leads to an increase in cell survival.[21]

In this study, the pasak bumi compounds are predicted to target the proteins that has a role in progression, metastasis, cell cycle, and proliferation in prostate cancer. The results from SWISS Target shows that the compounds in pasak bumi may interact with KDR, NFκB1, and bcl2. Meanwhile, the results in PASS server show that they may interact with p53. Furthermore, they interacted with the target protein, namely, PTEN.

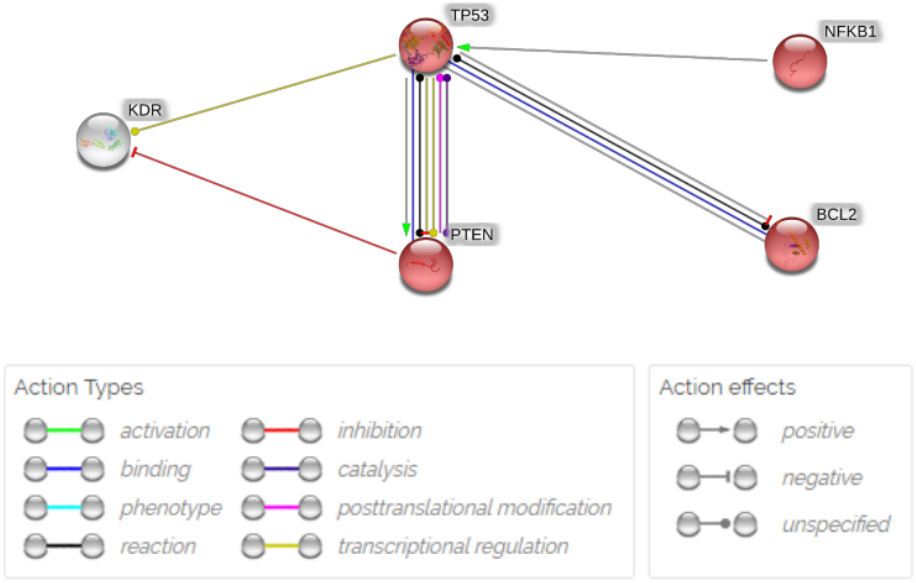

Fig.2:The interaction between target protein and PTEN. The red colour shows the proteins involved in prostate cancer that were recorded in the KEGG pathway.

This study suggests that pasak bumi may be used as a candidate for the treatment of prostate cancer, because it will increase the expression of p53. p53 has a role in DNA damage, therefore it affects the expression of PTEN that facilitates the elimination of cancer. Tumor suppressor p53

does not only play an important role in cell cycle, senescence, autophagy, and apoptosis, but it also regulates cell metabolism.[22] p53 inhibits aerobic glycolysis by inducing the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR),[23] or by decreasing the expression of glycolytic enzyme phosphoglycerate mutase 1 (PGAM1).[24] p53 shifts cell metabolism from the glycolytic pathway to the respiratory pathway through the synthesis of cytochrome C oxidase 2 (SCO2).[25] p53 also increases the mitochondrial respiration by inducing glutaminase 2 (GLS2,[26]). Besides, p53 may directly interact with glucose-6-phosphate dehydrogenase (G6PD) to suppress the pentose phosphate pathway.[27,28,29,30,31,32]

CONCLUSION

Pasak bumi can become a candidate for prostate cancer, because it increases the expression of p53. p53 has a role in DNA damage, and affects the expression of PTEN that facilitates the elimination of cancer.

REFERENCES

1. Qian B, Yao Y, Liu C, et al (2017). SU6668 modulates prostate cancer progression by down regulating MTDH/AKT signaling pathway. Int J Oncol, 50, 1601-11.
2. Akaza H Hinotsu S Cooperberg MRet al. Sixth joint meeting of J-CaP and CaPSURE—a multinational perspective on prostate cancer management and patient outcomes. Jpn J Clin Oncol 2013;43:56–66.
3. Brawley OW (2012). Prostate cancer epidemiology in the United States. World J Urol, 30, 195-200.
4. Mehdi Mirzaei-Alavijeh (2017) et al. Prevalence, cognitive and sosio-demographic determinant pf prostate cancer screening. Asian Pac J Cancer Prev, 19 (4), 1041-1046
5. Soh JYC, Hirai HW, Ho JMW, Chan FCH, Tsoi KKF, Ng CF (2019) Global incidence of prostate cancer in developing and developed countries with changing age structures. PLoS ONE 14(10): e0221775
6. Gao C, et all. Cytotoxic and chemosentizitation effect of Scutellarin from traditional chinesse herb Scutellaria altissima L. in human prostate cancer cells. Oncology Reports 38: 1491-1499, 2017
7. Wang Lei, et al. Hexokinase 2-mediated warburg effect is required for PTEN- and p53- deficiency-driven prostate cancer growth. Cell Reports 8, 1461–1474, September 11, 2014.
8. Ronen Shira, Abbott DanielW., Kravtsov Oleksandr, Abdelkader Amrou, Xu Yuyun, Banerjee Anjishnu, Iczkowski Kenneth A., PTEN loss and p27 loss differ among morphologic patterns of prostate cancer, including cribriform, Human Pathology (2017), doi: 10.1016/j.humpath.2017.04.024.
9. Deocampo ND, Huang H, Tindall DJ. The role of PTEN in the progression and survival of prostate cancer. Minerva Endocrinologica. 2003 Jun;28(2):145-153.
10. Calastretti, A., Gatti, G., Quaresmini, C., & Bevilacqua, A. (2014). Down-modulation of Bcl-2 sensitizes PTEN-mutated prostate cancer cells to starvation and taxanes. The Prostate, 74(14), 1411–1422. doi:10.1002/pros.22857.
11. Silalahi, M. Hubungan pemanfaatan tumbuhan pasak bumi(eurycoma longifolia, Jack) sebagai obat tradisional dan bioaktivitasnya. Jurnal Pendidikan Matematika dan IPA. 2019. Vol 10(2), h. 109-121
12. Ahmad, N, et all. Bioavailability of eurycomanone in its pure form and in a standardised Eu rycoma longifolia Water ex-tract. 2018. Pharmaceutics 10: 1-16.
13. George, A., Kawasaki, Y., and Abas, A. (2018). Eurycoma longifolia extract and its use in enhancing and/or stimulating immune system. Patent application Publication. Pub. No. US 2018/0153950 A1. Jun. 7, 2018: p: 1-16.
14. Hafiz M, et all. QUANTIFICATION OF 9-METHOXYCANTHIN-6-ONE AND ANTICANCER ACTIVITIES OF DIFFERENT PLANT PARTS OF EURYCOMA LONGIFOLIA. Proceedings of MAPS-15; 215-219 ,2018
15. Nurani L H and Mubarika S 2011 Mekanisme Molekuler Kemopreventif dan Antikanker Senyawa Aktif Akar Pasak Bumi (Eurycoma longifolia Jack) Kajian In vitro pada sel T47D dan In vivo pada Kanker Payudara pada Tikus SD yang diinduksi DMBA Universitas Gajah Mada
16. Chan K L, Choo C Y and Abdullah N R 2005 Semisynthetic 12-O-Acyl- and 1,15-Di-Oacyleurycomanones from Eurycoma longifolia as potential antimalarial Planta Med. 71 967-69
17. Silalahi, M. dan Nisyawati (2015). Etnobotani pasak bumi (eurycoma longifolia) pada etnis Batak, Sumatera Utara. Pros Sem Nas Masy Biodiv In-don. 1(4): 743-746.
18. Thu, H.E., Hussain, Z., Mohamed, I.N., and Shuid, A.N. (2017). Eurycoma longifolia, a promising suppressor of RANKLinduced differentiation and activation of osteoclasts: An in vitro mechanistic evaluation. Journal of Ayurveda and Inte-grative Medicine xxx: 1-11.
19. M.Y Nurhanan, Hawariyah LPA, Ilham AM, Shukri MAM. Cytotoxic effect of the root extract of eurycoma longifolia jack. Phytother. Res. 19, 994–996 (2005).
20. Tong KL, Chan KL, AbuBakar S, Low BS, Ma HQ, Wong PF (2015) The In Vitro and In Vivo Anti-Cancer Activities of a Standardized Quassinoids Composition from Eurycoma longifolia on LNCaP Human Prostate Cancer

Cells. PLoS ONE 10(3): e0121752. doi:10.1371/journal.pone.0121752.
21. Chendil D, Anindita D, Swatee D, Mohammed M, Mansoor MA. Par-4, A pro-apoptotic gene, inhibits radiation-induced NFκB activity and Bcl-2 expression leading to induction of radiosensitivity in human prostate cancer cells PC-3. Cancer Biology & Therapy 1:2, 152-160, March 2002.
22. Wang Lei, et al. Hexokinase 2-mediated warburg effect is required for PTEN- and p53- deficiency-driven prostate cancer growth. Cell Reports 8, 1461–1474, September 11, 2014.
23. Bensaad, K., Tsuruta, A., Selak, M.A., Vidal, M.N., Nakano, K., Bartrons, R., Gottlieb, E., and Vousden, K.H. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell 126, 107–120.
24. Kondoh, H., Lleonart, M.E., Gil, J., Wang, J., Degan, P., Peters, G., Martinez, D., Carnero, A., and Beach, D. (2005). Glycolytic enzymes can modulate cellular life span. Cancer Res. 65, 177–185.
25. Matoba, S., Kang, J.G., Patino, W.D., Wragg, A., Boehm, M., Gavrilova, O., Hurley, P.J., Bunz, F., and Hwang, P.M. (2006). p53 regulates mitochondrial respiration. Science 312, 1650–1653.
26. Hu, W., Zhang, C., Wu, R., Sun, Y., Levine, A., and Feng, Z. (2010). Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. Proc. Natl. Acad. Sci. USA 107, 7455–7460.
27. Jiang, P., Du, W., Wang, X., Mancuso, A., Gao, X., Wu, M., and Yang, X. (2011). p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. Nat. Cell Biol. 13, 310–316.
28. Achmad, M.H., Ramadhany, S., Ramadhany, Y.F. Resistivity Of Protein Kinase-B (Akt), Nf-Kb Transduction Obstacles, And Apoptosis Induction (Caspace -3, -9) As Anti-Proliferation And Anti-Cancer Of Burkitt's Lymphoma Using Flavonoid Fraction Of Ethyl Acetate From Ant Nest (Myrmecodia Pendans). Journal of Physics: Conference Series. https://iopscience.iop.org/article/10.1088/1742-6596/1341/7/072001/pdf . 2019. Pp. 1-11.
29. Achmad, H. Khairunnisa, P. Mardiana, Karni Aulia, A. Potentially Of Extracted Papua's Anthill (Myrmecodia pendans) As Antitumor To Emphasis The Expression Of Vascular Endothelial Growth Factor Cell Burkitt's Lymphoma Cancer, Asian Journal. of Microbiol. Biotech. Env Sc. © Global Science Publications pp. 108-112, Vol. 20, No. (1): 2018 . ISSN-0972-3005.
30. Achmad H , Sherly Horax, Sri Ramadhany, Irene Edith Rieuwpassa, Melyanti Sari, Hendrastuti Handayani, Marhamah F. Singgih, Sumintarti Sugiharto. 2019 . Anti-Cancer and Anti-Proliferation Activity of Ethyl Acetate Extract From Ant Nest (Myrmecodia pendans) in Burkitt's Lymphoma Cancer Cells. Pesquisa Brasileira em Odontopediatria e Clinica Integrada. ISSN 1519-0501, 19 (1): e4325.
31. Achmad H. Horax S, Ramadhany S, et.al. 2019. Resistivity of Ant Nest (Myrmecodia pendans) On Ethanol Fraction Burkitt's Lymphoma Cancer Cells (Invitro) Through Interleukin 8 Angiogenesis Obstacles (Il-8). Journal of International Dental and Medical Research ,. ISSN 1309-100X. Vol 12 No. (2) pp.516-523.
32. Hasanuddin A, Risnawatim Ekawati N, Wijaya A, Yuswatiningsuh E, Oktavianahutagaol I, Rosdiana, Nurhaedah, Srrtika D, Achmad H. alysis of Epidemiological Characteristics Associated with Non-Adherance to Treatment Leprae Paucibacillary Patients in Jeneponto District, South Sulawesi, Indonesia" in International Journal of Pharmaceutical Research; 2020; 12(2): 3724-3728.
33. Achmad H., Huldani, Carmelita A.B., Fauziah, Hidayah N., Bokov D. Antioxidant and antiviral potential of brown algae (Phaeophyceae). International Journal of Pharmaceutical Research. 2020; 3(12): 2117-2125. DOI: 10.31838/ijpr/2020.12.03.292
34. Achmad H., Sarina, Bokov D.O., Ramadhany Y.F., Kirichenko E.V., Markov A. The Impact of Using Antibiotic Drugs in Pediatric Dentistry. International Journal of Pharmaceutical Research. 2020; 4(12): 2901-2910. DOI: 10.31838/ijpr/2020.12.04.400 http://www.scopus.com/inward/record.url?eid=2-s2.0-85095790474&partnerID=fpDjhFsn http://www.ijpronline.com/ViewArticleDetail.aspx?ID=18024
35. Brovchenko B.V., Ermakova V.A., Bokov D.O., Shylina I.A., Demina N.B., Chernova S.V. Validation of an HPLC-UV procedure for determining the glycyrrhizic acid content in licorice roots. Pharmaceutical Chemistry Journal. 2020. 53 (12): 1168-1173. DOI: 10.1007/s11094-020-02142-w https://link.springer.com/article/10.1007%2Fs11094-020-02142-w http://www.scopus.com/inward/record.url?eid=2-s2.0-85081914748&partnerID=MN8TOARS
36. Sukmana B.I., Edyson, Thahir H., Achmad H., Huldani, Bokov D.O. Research review on secondary metabolite compounds of Mangifera casturi bark and their functions. International Journal of Pharmaceutical Research.2020; 3(12): 2155-2161. DOI: 10.31838/ijpr/2020.12.03.309 http://www.ijpronline.com/ViewArticleDetail.asp?ID=17079 \http://www.scopus.com/inward/record.url?eid=2-s2.0-85089431331&partnerID=MN8TOARS

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