In silico authentication of amygdalin as a potent anticancer compound in the bitter kernels of family Rosaceae

Zainab Ayaz a,b,1, Bibi Zainab a,b,1, Sajid Khan a, Arshad Mehmoond Abbasi b, Mohamed S. Elshikh c, Anum Munir a,d, Abdullah Ahmed Al-Ghamdi c, Amal H. Alajmi c, Qasi D. Alsubaie c, Abd El-Zaher M.A. Mustafa c,e,*

aDepartment of Bioinformatics, Govt. Post Graduate College Mandian Abbottabad, Pakistan
bDepartment of Environmental Sciences, COMSATS University Islamabad, Abbottabad Campus, 22060, Pakistan
cDepartment of Botany and Microbiology, College of Science, King Saud University, Riyadh, Saudi Arabia
dDepartment of Bioinformatics and Biosciences, Capital University of Science and Technology Islamabad, Pakistan
eBotany Department, Faculty of Science, Tanta University, Tanta, Egypt

1 First two authors' have equal contribution in research work and shares first authorship.

Article info

Article history:
Received 21 May 2020
Revised 15 June 2020
Accepted 23 June 2020
Available online 30 June 2020

Keywords:
Amygdalin
Modeling
Simulation
PI3K–AKT–mTOR
Ras pathways
Cancer

Abstract

Amygdalin a naturally occurring compound, predominantly in the bitter kernels of apricot, almond, apple and other members of Rosaceae family. Though, amygdalin is used as an alternative therapy to treat various types of cancer but its role in cancer pathways has rarely been explored yet. Therefore, present study was intended with the aim to investigate the alleged anti-cancerous effects of amygdalin specifically on PI3K–AKT–mTOR and Ras pathways of cancer in human body. Computational modelling and simulation techniques were used to assess the effect of amygdalin on PI3K-AKT-mTOR and Ras pathways using different level of dosage. It was observed that amygdalin had direct and substantial contribution to regulate PI3K-mTOR activities on threshold levels while the other cancer pathways were effected indirectly. Consequently, amygdalin is a down-regulator of a cancer within a specified amount and contribute considerably to reduce various types of cancer in human. Furthermore, in-vitro and in-vivo analyses of amygdalin could be of helpful to authenticate its pharmacological effects.

© 2020 the Deanship of Scientific Research at King Saud University for funding this work by research group No (RG-1441-484). Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

It is well established that naturally occurring compounds are less toxic than synthetic ones (Nisar et al., 2018; Koparde et al., 2019), and because of this plants and animals based natural products are attaining more attention (Chen et al., 2019). Chinese herbal drug “Taoren (Semen Persicae)” contains a primary monomer component i.e. amygdalin (Tanaka et al., 2014). In traditional Chinese medicines, this plant is used to treat asthma, bronchitis, emphysema, leprosy, colorectal cancer, leucoderma, coagulation, anti-inflammatory, as analgesic, neoplastic, thirst-quenching, antipyretic, antitussive as well as to improve microcirculatory disturbance effects (Zhang et al., 2018; Yang et al., 2014; Hwang et al., 2008; Chang et al., 2005).

Amygdalin, which is also known as vitamin B17 or Laetrile (Lv et al., 2017), is an aromatic cyanogenic compound that belongs to sub-class of carbohydrates and carbohydrate conjugates. Chemical formula of amygdalin is C20H27NO11, having molecular weight of 457.432 g/mol and D-mandelonitrile-beta-D-gentiobioside structure (Chang et al., 2006), as shown in Fig. 1. Structure of amygdalin is comprises of two molecules of glucose viz. benzaldehyde and hydrocyanic acid (Shim et al., 2000; Fukuda et al., 2003). Amygdalin is a cyanogenic glycoside, abundantly present in in the kernels of the various species of Rosaceae family such in the bitter seeds of apricot, apple, almond, peaches, cherries, plums, grains, millets, sprouts and nuts (Lv et al., Bolarinwa et al., 2014, 2017; Xu & Song, 2014; Hwang et al., 2008). It has been reported that...
seeds of Rosaceae fruits contain more amygdalin than endocarps and mesocarps (Lee et al., 2017). Laetrile which is a semi-conservative form of amygdalin was used as an anticancer agent in 1970s (Integrative, 2017). However, in the late 1970s and early 1980s, after clinically examination Laetrile was rejected by FDA for cancer treatment due to scarce clinically data evidence about its efficacy and toxicity (Moertel et al., 1982). However, it has been used in many parts of the world even FDA refusal (Song & Xu, 2014). In 1987, USA banned the import of amygdalin (Laetrile) in the country, afterwards its use was also banned in Europe (Curran, 1980), but its analgesic, anti-coagulation, anti-neoeplastic, anti-inflammatory as well as microcirculatory disturbance effects were reported. Numerous claims about amygdalin toxicity and beneficial effects were stated, including the treatment of cancer but these claims are not substantial to make the decision due to limited data availability (Saleem et al., 2018; Xu & Song, 2014; Moertel et al., 1981; Dorr & Paxinos, 1978; Ellison et al., 1978). In this context, present study was focused to analyze the effect of amygdalin on a PI3K–AKT–mTOR and Ras pathways in human. Diverse oncogenes and growth factor receptors stimulate the activity of PI3K and elevated PI3K signaling is considered a hallmark of cancer. AKT substrates are involved in cell proliferation, metabolism, survival and motility while the activation of mTOR, specifically mTORC1, is a key concern of tumor-associated alterations that even alter PI3K pathway. Homeostatically balance of PI3K-AKT-mTOR network is critical to prevent the abnormal cellular proliferation (Fruman et al., 2017). Moreover, abnormal activation of PI3K, AKT, Ras, Raf, ERK are already reported in multiple human cancers and are evoked to be an attractive therapeutic targets in a range of malignancies (Rozengurt et al., 2014). In this context, present study was focused to analyze the effect of amygdalin on a PI3K–AKT–mTOR and Ras pathways in human. Diverse oncogenes and growth factor receptors stimulate the activity of PI3K and elevated PI3K signaling is considered a hallmark of cancer. AKT substrates are involved in cell proliferation, metabolism, survival and motility while the activation of mTOR, specifically mTORC1, is a key concern of tumor-associated alterations that even alter PI3K pathway. Homeostatically balance of PI3K-AKT-mTOR network is critical to prevent the abnormal cellular proliferation (Fruman et al., 2017). Moreover, abnormal activation of PI3K, AKT, Ras, Raf, ERK are already reported in multiple human cancers and are evoked to be an attractive therapeutic targets in a range of malignancies (Rozengurt et al., 2014).

2. Material and methods

2.1. Selection of drug candidate

Amygdalin was selected as a potential drug candidate to be delivered because of its traditional use for the treatment of many diseases, particularly to treat cancer. This compound is considered as a therapeutics in many parts of the world but there are a lot of conflicts about its cyanide poisoning. Therefore, available literature is not significant enough to make the confirmatory statement about its anti-cancerous efficacy.

2.2. Drug data collection and toxicity assessment

In depth literature survey and Pubchem (https://pubchem.ncbi.nlm.nih.gov) were used for drug data collection. ProFox (http://tox.charite.de/protox_II/) was used for toxicity assessment and lethal dosage (LD50) prediction of drug (Amygdalin). The toxicity class ranges from 1 to 6, those which lie from 1 to 3 have high rates of toxicity while 4 to 6 are acceptable (Drwal et al., 2014).

2.3. Pathway designing

To analyze the effects of amygdalin on cancer, a pathway having multiple nodes such as TOR (target of rapamycin), PI3K (Phosphatidylinositol 3-kinase), RAS (belongs to a class of protein called small GTPase, which involved in transmitting signals) pathways were designed computationally using MATLAB. MATLAB a computational software was used to design a pathway (Fig. 2), having multiple nodes, which are involved in the abnormal regulation leading to cancer (Rozengurt et al., 2014). The computational demonstration can precisely construct and explain the complete observable facts. The constructed technical model defines the biochemical relationship between different nodes (genes) and the effect of the drug (amygdalin) in different time units. Specifically, mTORC1 functions as a catalytic subunit, to control cellular growth, translation, transcription, as well as autophagy and is the best inhibitor used in the cancer therapy (Sulaimanov et al., 2017; Liu et al., 2016; Laplante & Sabatini, 2012). Moreover, abnormal activation of PI3K, AKT, Ras, Raf, ERK are already reported in multiple human cancers and are evoked to be an attractive therapeutic targets in a range of malignancies (Rozengurt et al., 2014).

2.4. Species data collection

Assigned parameters of the species (proteins) required for simulation such as concentration, amount and molecular weight, were retrieved by online computational search engine ProtParam (https://web.expasy.org/protparam). Reaction values i.e. molecular weight of species and species reactions, and reaction properties.
like reaction name, quantities of species used by a reaction and whether reaction causes stimulation or inhibition (kon/koff) were assigned, as reported previously (Rozengurt et al., 2014). The species properties were assigned as variants having molecular weights. The minimum and maximum values were assigned automatically by the software, according to the designed pathways.

2.5. Drug properties and dose

Pubchem and ProtParam databases were used as a search engine for collection of the drug properties. The drug properties were assigned in a model parameter having molecular weight distribution phase mean clearance phase hydrogen bond donor hydrogen bond acceptor rotatable bonds and xLogP.

2.6. Simulation

A computational model was developed, which mimics the in vivo simulations. Furthermore, we explain the robustness for systemic modulating behavior of amygdalin during the course of different time unit simulation. Time as well as quantities were adjusted in the add task menu and then model simulations were executed. Analysis was done on the model by adjusting different model conditions as well as comparing the model simulation before and after drug dosage to analyze whether the drug causes up regulation or down regulation of cancer.

3. Results and discussion

Because of proficient outcomes, time saving and cost effective properties, computational (in silico) techniques have attained more consideration in recent years. Over the last decade, these techniques are contributing significantly in PK/PD modeling, hypothesis prediction, drug analysis and for generation of biological model and their testing prior to in vivo and clinical studies (Pichardo-Almarza & Diaz-Zuccarini, 2016; Ekins et al., 2007). In past over 20% drugs were rejected because of toxicity but now computational analysis is making it easy for predicting the toxicity of drug candidates. Same is in the case of amygdalin, which is used to treat different types of cancer but at the same time it is considered toxic to human and banned in some countries like US and UK. Moreover, in silico analysis of this compound has rarely been done. Therefore, present study was focused on the toxicity assessment and role of amygdalin on PI3K–AKT–mTOR and Ras cancer pathways in human as shown in Fig. 2.

Results of drug properties and relevant information as reported previously (Ames et al., 1981) are given in Table 1. Toxicity analysis done by ProTox revealed that oral toxicity of drug (amygdalin) lied in a class 4 while its predicted LD50 was 405 mg/kg (Fig. 3). The toxicity class ranges from 1 to 6, those which lie from 1 to 3 have high rates of toxicity while 4 to 6 are acceptable (Drwal et al., 2014).

The specie properties were assigned as variants having molecular weights (Fig. 4). The minimum and maximum values were assigned automatically according to the designed pathway.
Pathways designed in simbio module of MATLAB (Rozengurt et al., 2014), having 12 inhibitory and 19 stimulatory reactions were interconnected to each other. Due to its robust properties, integrated pathways help minimize the effects of external perturbation on entire systems. At given rate kinetics, each functional species in the pathways is considered as node and linked to other important nodes (Lehar et al., 2008). Simulation task was applied to analyze the behavior of amygdalin on multiple cancerous nodes. Simulation analyses, which can be used to compare the results of high-throughput experiments, can be carried out with the exploration of the completed reaction plots. When comparing the experimental system with the significance of the results of the pathway model simulation, high validity of the overall mechanism prediction is produced. The actual biological process occurring inside cells can be observed and exploited to predict the individual organism’s novel properties and capabilities using this valid model (Chong et al., 2014). The simulation graphs of all the species which were involved in a designed pathway are given in Fig. 5.

To analyze the exact behavior of PI3K, AKT, mTOR and Ras nodes, distinct stimulatory tasks were applied. According to Hill et al., 2014; Thorpe et al., 2015, up-regulation of PI3K occurs during cancer, and we observed that threshold value of amygdalin (250 mL), worked effectively to down-regulate the PI3K. In cancer pathway, the observed maximum concentration of PI3K is $5.1 \times 10^4$ mL and minimum is $3.3 \times 10^4$ mL (Fig. 6a). After applying of the amygdalin dose, a decrease in the concentration of PI3K was observed within 12hr, which almost reached to the concentration of $1.0 \times 10^4$ within 10 days (Fig. 6b).

The mTOR deregulation causes pathophysiological conditions involving aging, Alzheimer’s disease, diabetes, obesity and cancer (Hua et al., 2019). The mTORC1 involves in the protein synthesis, cell mass increase, lipid accumulation and cellular energy (Zoncu et al., 2011). In the study model, mTORC1 concentration was $0.9 \times 10^4$ per day when no dose of amygdalin was applied, and was decreasing progressively. And within 10 days the concentra-
tion of mTORC1 reaches to zero. However, an exponential upsurge was observed in the concentration of mTORC1 after applying amygdalin dose (250 mL) as shown in Fig. 7 a&b.

Active-site inhibitors enhance the activity of ERK by its over-activation and ERK concentration was found higher in cancer patients (Soares et al., 2013). Amygdalin dose shows no effect on the activity of ERK, even the dose value was increased up to 400 mL (Fig. 8 a&b).

Akt is over-regulated in cancer pathways. Amygdalin dose shows neither increase nor decrease to the Akt pathway directly even the dose amount was increased up to 400 mL (Fig. 9 a&b), but it is effective indirectly by applying the dose to PI3K which is inter-connected to Akt (Mendoza et al., 2011).

Ras signaling pathways have been detected in association with a variety of cancers (Fernández-Medarde and Santos, 2011). Drug dose was applied directly on Ras node and value was set to be 300 mL, but no effect on Ras activity was observed (Fig. 10 a&b).

4. Conclusion:

Computational techniques have gained significant importance due to their proficient results. In the present study, computational technique was used to analyze the effect of amygdalin on interconnected carcinogenic pathways. The initial value of dosage (250 mL), contributed significantly in the down-regulation of cancer by effecting PI3K and mTOR pathways, which consequently effect to other carcinogenic pathways circuitously. However, amygdalin effects on ERK, Ras and AKT pathways were comparatively less, even dose value was increased. Therefore, we suggest...
Fig. 7. (a) mTORC1 graph without dose, (b) increase of mTORC1 by applying dose.

Fig. 8. (a) ERK graph without any dose (b) ERK graph with dose (250 mL).

Fig. 9. (a) Akt graph without dose, (b) Akt graph with dose of 400 mL.
that natural sources of amygdalin i.e. bitter kernels could be used in a specified amount to treat various types of cancer in human. In Addition, in vivo and in vitro studies could be helpful to authenticate the use of amygdalin for cancer therapy.

Acknowledgement

All authors are grateful to the Deanship of Scientific Research at King Saud University Saudi Arabia for financial support through project No RG-1441-484. Moreover, lab facilities provided by Department of Bioinformatics, Govt. Post Graduate College Mandian Abbottabad and COMSATS University Islamabad, Abbottabad Campus are thankfully acknowledged.

Declaration of Competing Interest

None of the authors have any challenging conflict of interests.

References

Ames, M.M., Moyer, T.P., Kovach, J.S., Moertel, C.G., Rubin, J., 1981. Pharmacology of amygdalin (laetrile) in cancer patients. Cancer Chemother. Pharmacol. 6 (1), 51–57.

Bolarinwa, I.F., Orfila, C., Morgan, M.R.A., 2014. Amygdalin content of seeds, kernels and food products commercially-available in the UK. Food Chem. 152, 133–139.

Chang, H.K., Yang, H.Y., Lee, T.H., Shin, M.C., Lee, M.H., Shin, M.S., Cho, S., 2005. Armeniaca semen extract suppresses lipopolysaccharide-induced expressions of cyclooxygenase-2 and inducible nitric oxide synthase in mouse BV2 microglial cells. Biol. Pharm. Bull. 28 (3), 449–454.

Chang, H.K., Shin, M.S., Yang, H.Y., Lee, J.W., Kim, Y.S., Lee, M.H., et al., 2006. Amygdalin induces apoptosis through regulation of Bax and Bcl-2 expressions in human DU145 and LNCaP prostate cancer cells. Biol. Pharm. Bull. 29 (8), 1597–1602.

Chen, Y., Al-Ghamdi, A.A., Elshikh, M.S., Shah, M.H., Al-Desary, M.A., Abbas, A.M., 2019. Phytochemical profiling, Antioxidant and HepG2 cancer cells’ anti-proliferation potential in the kernels of apricot cultivars. Saudi J. Biol. Sci. Curran, W.J., 1980. Laetrile for the terminally ill: Supreme Court stops the nonsense. Dobscheck, T.S., Zhang, L., Yoon, J., Costa, J., 2009. In silico cancer modeling: is it ready for prime time? Nat. Clin. Pract. Oncol. 6 (1), 34–42. https://doi.org/10.1038/ncomponc1237.

Dorr, R.T., Paxinos, J., 1978. The current status of laetrile. Ann. Intern. Med. 89 (3), 389–397.

Downward, J., 2003. Targeting Ras signalling pathways in cancer therapy. Nat. Rev. Cancer 3 (1), 11–22.

Drwal, M.N., Banerjee, P., Dunkel, M., Wettig, M.R., Preissner, R., 2014. ProTox: a web server for the in silico prediction of rodent oral toxicity. Nucleic Acids Res. 42 (W1), W53–W58.

Ekins, S., Mestres, J., Testa, B., 2007. In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. Br. J. Pharmacol. 152 (1), 9–20.

Ellison, N.M., Byar, D.P., Newell, C.R., 1978. Special report on Laetrile: the NCI Laetrile review: results of the National Cancer Institute’s retrospective Laetrile analysis. N. Engl. J. Med. 299 (10), 549–552.

Fernández-Medarde, A., Santos, E., 2011. Ras in cancer and developmental diseases. Genes Cancer 2 (3), 344–358.

Fruman, D.A., Chiu, H., Hopkins, B.D., Bagrodia, S., Cantley, L.C., Abraham, R.T., 2017. The PI3K pathway in human disease. Cell 170 (4), 605–635.

Fukuda, T., Ito, H., Mukainaka, T., Tokuda, H., Nishino, H., Yoshida, T., 2003. Anti-tumor promoting effect of glycosides from Prunus persica seeds. Biol. Pharm. Bull. 26 (2), 271–273.

Hill, R., Kalathur, R.K.R., Callejas, S., Coelho, L., Brandão, R., Sereide, B., Dopazo, A., 2014. A novel phosphatidylinositol-3-kinase (PI3K) inhibitor directs a potent FOXO-dependent, p53-independent cell cycle arrest phenotype characterized by the differential induction of a subset of FOXO-regulated genes. Breast Cancer Res. 16 (6), 482.

Hosseini, L., Gajal, A., Bumbaca Yadav, D., Sukumaran, S., Ramanujan, S., Paxson, R., Gaddkar, K., 2018. CPKPDSim: a SimBiology®-based GUI application for PKPD modeling in drug development. J. Pharmacokinet. Pharmacodyn. 45 (2), 259–275.

Hua, H., Kong, Q., Zhang, H., Wang, J., Luo, T., Jiang, Y., 2019. Targeting mTOR for cancer therapy. J. Hematol. Oncol. 12 (1), 71.

Hwang, H.J., Kim, P., Kim, C.J., Lee, H.J., Shin, I., Yin, C.S., et al., 2008. Antinociceptive effect of amygdalin isolated from Prunus armeniaca on formalin-induced pain in rats. Biol. Pharm. Bull. 31 (8), 1559–1564.

Integrative, P.D.Q., 2017. Laetrile/Amygdalin (PDQ®). In PDQ Cancer Information Summaries [Internet]. National Cancer Institute (US).

Khim Chong, C., Saberi Mohammad, M., Deris, S., Shahir Shamsir, M., Wen Chooy, Y., En Chai, L., 2014. A review on modelling methods, pathway simulation software and recent development on differential evolution algorithms for metabolic pathways in systems biology. Curr. Bioinform. 9 (5), 509–521.

Koparde, A.A., Doijad, R.C., Magdum, C.S., 2019. Natural products in drug discovery. In: Pharmacognosy-Medicinal Plants. InteOpen.

Laplante, M., Sabatini, D.M., 2012. mTOR signaling in growth control and disease. Cell 149 (2), 274–293.

Lee, S.-H., Oh, A., Shin, S.-H., Kim, H.-N., Kang, W.-W., Chung, S.-K., 2017. Amygdalin contents in peaches at different fruit development stages. Prevent. Nutrit. Food Sci. 22 (3), 237.

Lehar, J., Krueger, A., Zimmermann, G., Borsi, A., 2008. High-order combination effects and biological robustness. Mol. Syst. Biol. 4, 215.

Lv, J., Xiong, W., Lei, T., Wang, H., Sun, M., Hao, E., Wang, Y., 2017. Amygdalin ameliorates the progression of atherosclerosis in LDL receptor-deficient mice. Mol. Med. Rep. 16 (6), 5087.

Lv, J., Xiong, W., Lei, T., Wang, H., Sun, M., Hao, E., Wang, Y., 2017. Amygdalin ameliorates the progression of atherosclerosis in LDL receptor-deficient mice. Mol. Med. Rep. 16 (6), 8171–8179.

Mendoza, M.C., Er, E.E., Blenis, J., 2011. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem. Sci. 36 (6), 320–328.

Moertel, C.G., Ames, M.M., Kovach, J.S., Moyer, T.P., Rubin, J.R., Tinker, J.H., 1981. A pharmacologic and toxicological study of amygdalin. JAMA 245 (6), 591–594.

Moertel, C.G., Fleming, T.R., Rubin, J., Koval, L.K., Sarna, G., Koch, R., et al., 1982. A randomized clinical trial of amygdalin (Laetrile) in the treatment of human cancer. N. Engl. J. Med. 306 (4), 201–206.

Nisar, B., Sultan, A., Rubah, S.L., 2018. Comparison of medicinally important natural products versus synthetic drugs-A short commentary. Nat. Prod. Chem. Res. 6 (2), 308.
Pichardo-Almarza, C., Diaz-Zuccarini, V., 2016. From PK/PD to QSP: understanding the dynamic effect of cholesterol-lowering drugs on atherosclerosis progression and stratified medicine. Curr. Pharm. Des. 22 (46), 6903–6910.

Rozengurt, E., Soares, H.P., Sinnett-Smith, J., 2014. Suppression of feedback loops mediated by PI3K/mTOR induces multiple overactivation of compensatory pathways: an unintended consequence leading to drug resistance. Mol. Cancer Ther. 13 (11), 2477–2488.

Saleem, M., Asif, J., Asif, M., Saleem, U., 2018. Amygdalin from apricot kernels induces apoptosis and causes cell cycle arrest in cancer cells: an updated review. Anti-Cancer Agents Med. Chem. (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 18 (12), 1650–1655.

Shim, B.S., Choi, S.H., Park, J.K., 2000. Study on toxicity, anti-cancer and NK cell activity of Lateril oil. J. Korean Orient. Oncol. 6 (1), 19–28.

Soares, H.P., Ni, Y., Kisfalvi, K., Sinnett-Smith, J., Rozengurt, E., 2013. Different patterns of Akt and ERK feedback activation in response to capamycin, active-site mTOR inhibitors and metformin in pancreatic cancer cells. PLoS ONE 8 (2).

Song, Z., Xu, X., 2014. Advanced research on anti-tumor effects of amygdalin. J. Cancer Res. Ther. 10 (5), 3.

Sulaimanov, N., Klose, M., Busch, H., Boerries, M., 2017. Understanding the mTOR signaling pathway via mathematical modeling. Wiley Interdiscip. Rev. Syst. Biol. Med. 9, (4) e1379.

Tanaka, R., Nitta, A., Nagatsu, A., 2014. Application of a quantitative 1H-NMR method for the determination of amygdalin in Persicae semen, Armeniacae semen, and Mume fructus. J. Nat. Med. 68 (1), 225–230.

Thorpe, L.M., Yuzugullu, H., Zhao, J.J., 2015. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat. Rev. Cancer 15 (1), 7–24.

Xu, X., Song, Z., 2014. Advanced research on anti-tumor effects of amygdalin. J. Cancer Res. Ther. 10 (5), 3.

Yang, C., Zhao, J., Cheng, Y., Li, X., Rong, J., 2014. Bioactivity-guided fractionation identifies amygdalin as a potent neurotrophic agent from herbal medicine Semen Persicae Extract. Biomed Res. Int. 2014, 1–10.

Zhang, X., Hu, J., Zhuo, Y., Cui, L., Li, C., Cui, N., Zhang, S., 2018. Amygdalin improves microcirculatory disturbance and attenuates pancreatic fibrosis by regulating the expression of endothelin-1 and calcitonin gene-related peptide in rats. J. Chinese Med. Assoc. 81 (5), 437–443. https://doi.org/10.1016/j.jcma.2017.09.005.

Zoncu, R., Efeyan, A., Sabatini, D.M., 2011. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat. Rev. Mol. Cell Biol. 12 (1), 21.

Further Reading

Danhof, M., Delange, E., Dellapasqua, O., Ploeger, B., Voskuyl, R., 2008. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trends Pharmacol. Sci. 29 (4), 186–191.