REVIEW ARTICLE
Eurasian J Bio Chem Sci, 5(Suppl 1):162-165, 2022
https://doi.org/10.46239/ejbcs.1130645

EJBCS

Eurasian Journal of Biological and Chemical Sciences

Journal homepage: www.dergipark.org.tr/ejbcs

Phenolic compounds that modulate the multi drug resistance through inhibiting of P-glycoprotein encoded by gene ABCB1

Onder Yumrutas[1*], Pınar Yumrutas[2]

*[*1] University of Adıyaman, Faculty of Medicine, Department of Medical Biology, 02200, Adıyaman-Türkiye*
[2] University of Gaziantep, Faculty of Medicine, Department of Respiratory Disease and Cancer Biology, 27410, Gaziantep-Türkiye

*Corresponding author : yumrutasonder@gmail.com
Orcid No: https://orcid.org/0000-0001-9657-8306

Received : 15/06/2022
Accepted : 16/10/2022

Abstract: One of the most important challenges in the fight against cancer is acquired/multi drug resistance. P-glycoprotein (P-gp), encoded by gene ABCB1 (or MDR1) in many organs, is one of the important factors involved in the development of drug resistance. P-gp is mainly involved in efflux of toxic substances such as xenobiotics from the cell. Also, it plays a role the efflux of drugs used in the treatment of cancer, and so, it reduces the rate of success in cancer treatment. Phenolic compounds are chemicals that are naturally synthesized in plants and have many biological activities such as especially antioxidant and anticancer. In previous studies, it was determined that in addition to anticancer activities of the phenolic compounds, they modulate the multi drug resistance by inhibiting the expression and function of P-gp. In this review, phenolic compounds that play a role in modulating the multi-drug resistance by inhibiting the activation and expression of P-gp are discussed.

Keywords: Cancer, multi drug resistance, phenolics, P-glycoprotein, ABCB1, MDR1

1. Introduction

Cancer resistance

Cancer is a disease that has been trying to cure for a long time. Millions of people die every year because of the cancer (Sung et al. 2021). In cancer treatment, applications such as chemotherapy, radiotherapy and surgery are basically used. (Jaklitsch et al. 2003; Chabner and Roberts 2005; Kaur et al. 2011). Among these methods, the chemotherapy is used first for the basic inhibition of proliferation, invasion, and metastasis on cancer cells. Despite the positive effects of drugs used for cancer treatments, in some cases there is a resistance to these drugs and the drugs used are excreted from cancer cells by different mechanisms (Gottesman et al. 2002). Because of this efflux, the fight against cancer can be significantly inhibited.

Multi-drug resistance (MDR) pumps serve in the efflux of cancer drugs. These proteins generally play an important defense role when cells are exposed to xenobiotics. While these proteins usually take part in the efflux of toxic substances out of the cell, they can also take part in the removal of different substances (Gottesman et al. 2002). This system also captures the chemotherapeutic agents applied to cancer cells as a foreign substance and immediately sends them out of the cell. Therefore, resistance to chemotherapeutic agents is acquired in cancer cells.

Targeting of P-glycoprotein in modulation of MDR

ATP dependent pumps send many of substrate compounds out of cells to prevent toxicity in many cells (Ford and Beis 2019). The most known of these transporters is P-glycoprotein (P-pg) which is one of the first members described of a large family of ATP-dependent transporters known as the ATP-binding cassette (ABC) family and it is encoded by the ABCB1 (MDR1) gene. P-gp is a protein consisting of two nucleotide binding and two drug binding domains (Gillet and Gottesman 2009; Mollazaleh et al. 2018). There are many studies showing the roles of this efflux pump in cancer resistance (Waghray and Zhang 2017; Shi et al. 2020; Huang et al. 2021).

The P-gp is expressed in most cancer cells. Although P-gp is inhibited by synthetic blocker compounds such as verapamil and cyclosporin (Sikic et al. 1997), undesirable side effects may occur for normal cells due to these compounds. Moreover, it is very interesting that natural compounds and herbal drugs have less side effects than synthetics and have versatile effects at appropriate doses. In previous studies, it has been reported that these transport proteins are suppressed using phytochemicals together with cancer drugs and chemotherapeutic agents remain in cancer cells (Molnár et al. 2010; Teng et al. 2021; Teng et al. 2022).

There are many studies showing the inhibitory effects of plant extracts and phytochemicals on cancer cells (Yumrutas et al. 2015; Yumrutas et al. 2018; Cocelli et al. 2021). It has been proven that isolated phytochemicals are responsible for many biological activities and can also be used in the prevention of cancer by acting on the molecular pathways involved in the pathogenesis of cancer. (Saklani and Kutty 2008). The effects of natural compounds in modulating the multidrug resistance have been discovered as well as inhibition of proliferation of cancer cells, induction of apoptosis, arresting of cell cycle and induction of ROS.

Among the most well-known of these compounds, phenolic compounds have been demonstrated to have biological activities including anticancer (Yumrutas et al. 2018), antioxidant (Erkan et al. 2008), anti-inflammatory (Rocha et al. 2015), antimicrobial (Mandal et al. 2017), wound healing (Ozay et al. 2019). Phenolic compounds include many kind such as flavonoids, lignans, phenolic acids, stilbenes and tannins (Amarowicz and Pegg 2019)

The multi drug resistance can lead to the increased drug absorbance, increased drug efflux, altered drug metabolism, altered treatment target and apoptotic pathway, epigenetic changes, and differences in tumor microenvironment (Holohan et al. 2013; Whang et al. 2019; Zheng et al. 2021). To reduce these effects, it is thought that the increase in the discover of active compounds such as phenolics will significantly support the fight against cancer.

Phenolic compounds that modulates the MDR

Phenolic compounds are secondary compounds synthesized in almost all plants. These compounds are synthesized via the shikimic acid and phenylpropanoid pathway (Laura et al. 2019). Many biological activities of phenolic compounds have been studied for many years. Antioxidant activity is among the most well-known activities (Shahidi and Ambigaipalan, 2015). They exhibit important biological activities by acting on the factors involved in many pathways. Therefore, they exhibit important biological activities (Xu et al., 2021; Roleira et al. 2015; de Oliveira et al. 2021). Phenolic compounds have been determined the roles in modulating of drug resistance in cancer cells and their mechanisms of action on P-gp are mentioned below:

5-hydroxy-7,8-dimethoxyflavanone:5-hydroxy-7,8-dimet hoxyflavanone is a flavonoid compound derived from *Fissistigma cupreonitens* (Theng et al., 2021). It was reported that it significantly inhibited function of P-gp at a concentration of 2.5 μg/ml. Therefore, it modulated the MDR inhibiting the efflux of doxorubicin, a drug which being used in cancer treatment, out of the cancer cells. Also, MDR was decreased in the multidrug resistant cervical cancer cell line KB/VIN exposed to Vincristine, Paclitaxel, and Doxorubicin (Theng et al., 2021) in a dose dependent manner.

Kaempferol: It is an important flavonol found in many plants. It suppressed P-gp expression and significantly inhibited its activity in multi-drug resistant cancer cells (KB-V1). However, it increased intracellular drug accumulation. In addition, extracellular efflux of vinblastine was significantly reduced. (Limptrakul et al., 2005).

Cinnamophilin: It is a phenolic lignan obtained from *Cinnamomum philippinense*. In a previous study, when given with drugs such as docetaxel, vincristine, and paclitaxel, it provided modulation of MDR. In addition, the efflux function of p-gb was significantly inhibited and therefore the efflux of doxorubicin was also inhibited (Theng et al. 2021b).

Silychristin A ve 2,3-dehydrosilychristin A: Silychristin A and 2,3-dehydrosilychristin A are the second most abundant derivatives of silymarin. Dose-dependent inhibition of P-gp was observed after administration of silychristin A and 2,3-dehydrosilychristin A. In addition, drug sensitivity was decreased in doxorubicin-resistant ovarian cancer cells. In the same study, the anhydro- and iso- derivatives of silychristin A, In addition to Silychristin A and 2,3-dehydrosilychristin A, not only inhibited the function of P-gp but also reduced its expression (Viktorová et al., 2019).

Caffeic acid: Teng et al (2020) reported that exposure of ABCB1/Flp-InTM-293 and KB/VIN cells with multi-drug resistance to caffeic acid causes inhibition of p-gb protein and reverses MDR resistance. In addition, it was stated that this effect was demonstrated by caffeic acid's binding to P-gp via GLU74 and TRY117 residues.

Procyanidin (catechin-3-O-2-leucocyanidin): It is a polyphenol flavonoid compound found in many fruits and vegetables. In a previous study conducted with human ovarian multidrug resistant subline (A2780) cell line, it was determined that the cell viability was significantly reduced after the application of dose-dependent procyanidin given with paclitaxel and adriamycin. In addition, Procyanidin down-regulated the mRNA and protein expression of MDR1 in resistant A2780 cells through NF-kB inhibition. In addition, MDR1 was suppressed by time-dependent inhibition of YB-1 nuclear translocation through inhibition of the MAP/ERK pathway in A2780/T cells treated with procyanidin (Zhao et al., 2013).

Emodin (1, 3, 8-trihydroxy-6-methylanthra-quinone) and Rhein: Emodin and Rhein are members of anthraquinones, a subgroup of phenolic compounds. (Teng et al, 2022). In a previous study, it observed a decrease the P-gp protein expression in adriamycin-resistant K562/ADM cells. It was stated that P-gp can bind to the R-site, reducing the function of P-gp and reversing MDR (Min et al., 2017). Moreover, Rhein was involved in the correction/modulation of MDR by causing downregulation of P-gp in KB/VIN cells. (Teng et al, 2022).

Conclusion

The roles of phenolics in the elimination of acquired resistance caused by chemotherapeutic agents used in the treatment of cancer have been proven in many studies. In particular, when the effects of phenolics on P-gp expression and function are evaluated, it is thought that the use of these

compounds together with chemotherapeutic agents in the clinic will have important effects. However, most of the studies showing the relationship between phenolic compounds and P-gp have been run by using the cell experiments. In order to evaluate the effects of phenolics on P-gp, the number of in vivo experiments should be also increased. In addition, phenolics can be effluxed by ABC pumps, and this should be taken into account in future studies.

Authors' contributions: ÖY and PY contributed equally to the preparation of this review.

Conflict of interest disclosure: Authors declare no any conflict of interest

References

Amarowicz R, Pegg RB. 2019. Natural antioxidants of plant origin. In Advances in food and nutrition research (Vol. 90, pp. 1-81). Academic Press.

Chabner BA, Roberts TG. 2005. Chemotherapy and the war on cancer. Nat Rev Cancer. 5: 65-72.

Cocelli G, Pehlivan M, Yumrutas O. 2021. Sideritis perfoliata inhibits cell proliferation, induces apoptosis and exhibits cellular antioxidant activity in cervical cancer cells. BLACPMA. 20(4).

de Oliveira EF, Yang X, Basnayake N, Huu CN, Wang L, Tikekar R, Nitin N. 2021. Screening of antimicrobial synergism between phenolic acids derivatives and UV-A light radiation. Journal of Photochemistry and Photobiology B: Biology. 214: 112081.

Erkan N, Ayranci G, Ayranci E. 2008. Antioxidant activities of rosemary (Rosmarinus Officinalis L.) extract, blackseed (Nigella sativa L.) essential oil, carnosic acid, rosmarinic acid and sesamol. Food Chem. 110: 76-82.

Ford RC, Beis K. 2019. Learning the ABCs one at a time: structure and mechanism of ABC transporters. Biochem Soc Trans 47: 23-36.

Gillet JP, Gottesman MM. 2009. Mechanisms of Multidrug Resistance in Cancer. Multi-Drug Resistance in Cancer. 47-76.

Gottesman MM. 2002. Mechanisms of cancer drug resistance. Annu Rev Med. 53: 615-627.

Holohan S, Van Schaeybroeck DB, Longley PG. 2013. Johnston, Cancer drug resistance: an evolving paradigm. Nat Rev. Cancer. 13: 714-726

Huang Y, Zhang J, Zhang Y, Shi L, Qin X, Lu B, Ding Y, Wang Y, Chen T, Yao Y. 2021. P-glycoprotein suppression by photothermal-responsive nitric oxide releasing nanoplatform for triple-combination therapy of multidrug resistant cancer. Mater Des. 211:110160.

Jaklitsch MT, Mery CM, Audisio RA. 2003. The use of surgery to treat lung cancer in elderly patients. Lancet Oncol. 4: 463-471.

Kaur P, Hurwitz MD, Krishnan S, Asea A. 2011. Combined hyperthermia and radiotherapy for the treatment of cancer. Cancers. 3: 3799-3823.

Laura A, Moreno-Escamilla JO, Rodrigo-García J, Alvarez-Parrilla E. 2019. Phenolic compounds. In *Postharvest physiology and biochemistry of fruits and vegetables* (pp. 253-271). Woodhead Publishing.

Limtrakul P, Khantamat O, Pintha K. 2005. Inhibition of P-glycoprotein function and expression by kaempferol and quercetin. J Chemotherapy. 17: 86-95.

Mandal SM, Dias RO, Franco OL. 2017. Phenolic compounds in antimicrobial therapy. J Med Food. 20: 1031-1038.

Min H, Niu M, Zhang W, Yan J, Li J, Tan X, Li B, Su M, Di B, Yan F. 2017. Emodin reverses leukemia multidrug resistance by competitive inhibition and downregulation of P-glycoprotein. PLoS ONE 12: e0187971

Mollazadeh S, Sahebkar A, Hadizadeh F, Behravan J, Arabzadeh, S. 2018. Structural and functional aspects of P-glycoprotein and its inhibitors. Life Sci. 214:118-123.

Molnár J, Engi H, Hohmann J, Molnár P, Deli J, Wesolowska O, Michalak K, Wang Q. 2010. Reversal of multidrug resistance by natural substances from plants. Curr Top Med Chem.10: 1757-1768.

Özay Y, Güzel S, Yumrutaş Ö, Pehlivanoğlu B, Erdoğdu İH, Yildirim Z, Turk BA, Darcan S. 2019. Wound healing effect of kaempferol in diabetic and nondiabetic rats. J Surg Res. 233: 284-296.

Roleira FM, Tavares-da-Silva EJ, Varela CL, Costa SC, Silva T, Garrido J, Borges F. 2015. Plant derived and dietary phenolic antioxidants: Anticancer properties. Food Chemistry. 183: 235-258.

Rocha J, Eduardo-Figueira M, Barateiro A, Fernandes A, Brites D, Bronze R, Duarte CMM, Serra AT, Pinto R, Freitas M, Fernandes E, Silva-Lima B, Mota-Flipe H, Sepodes B. 2015. Anti-inflammatory effect of rosmarinic acid and an extract of Rosmarinus officinalis in rat models of local and systemicinflammation. Basic Clin Pharmacol Toxicol. 116: 398-413.

Saklani A, Kutty SK. 2008. Plant-derived compounds in clinical trials. Drug Discov. Today. 13, 161-171.

Shahidi F, Ambigaipalan P. 2015. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects–A review. Journal of functional foods. 18: 820-897.

Shi X, Valizadeh A, Mir SM, Asemi Z, Karimian A, Majidina M, Safa A, Yosefi B. 2020. miRNA-29a reverses P-glycoprotein-mediated drug resistance and inhibits proliferation via up-regulation of PTEN in colon cancer cells. Eur J Pharmacol: 880:173138.

Sikic BI, Fisher GA, Lum BL, Halsey J, Beketic-Oreskovic L, Chen G. 1997. Modulation and prevention of multidrug resistance by inhibitors of P-glycoprotein. Cancer Chemother Pharmacol. 40: S13-S19.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 71: 209-249.

Teng YN, Huang BH, Huang SY, Wu IT, Wu TS, Lee TE, Hung CC. 2021. Cinnamophilin overcomes cancer multi-drug resistance via allosterically modulating human P-glycoprotein on both drug binding sites and ATPase binding sites. Biomed Pharmacother. 144: 112379.

Teng, YN, Kao MC, Huang SY, Wu TS, Lee TE, Kuo CY, Hung CC. 2022. Novel application of rhein and its prodrug diacerein for reversing cancer-related multidrug resistance through the dual inhibition of P-glycoprotein efflux and STAT3-mediated P-glycoprotein expression. Biomed Pharmacother. 150: 112995.

Teng YN, Lin KI, Lin YC, Thang TD, Lan YH, Hung CC. 2021. A novel flavonoid from Fissistigma cupreonitens, 5-hydroxy-7, 8-dimethoxyflavanone, competitively inhibited the efflux function of human P-glycoprotein and reversed cancer multi-drug resistance. Phytomedicine. 85: 153528.

Teng YN, Wang CC, Liao WC, Lan YH, Hung CC. 2020. Caffeic acid attenuates multi-drug resistance in cancer cells by inhibiting efflux function of human P-glycoprotein. Molecules. 25: 247.

Viktorová J, Dobiasová S, Řehořová K, Biedermann D, Káňová K, Šeborová K, Václavíková R, Valentová K, Ruml T, Křen V, Macek T. 2019. Antioxidant, anti-inflammatory, and multidrug resistance modulation activity of silychristin derivatives. Antioxidants. 8: 303.

Waghray D, Zhang Q. 2017. Inhibit or evade multidrug resistance P-glycoprotein in cancer treatment: miniperspective. J Med Chem. 61:5108-5121.

Xu QN, Zhu D, Wang GH, Lin T, Sun CL, Ding R, Tian WJ, Chen HF. 2021. Phenolic glycosides and flavonoids with antioxidant and anticancer activities from Desmodium caudatum. Natural Product Research. 35: 4534-4541.

Yumrutas O, Oztuzcu S, Pehlivan M, Ozturk N, Poyraz IE, Iğci YZ, Cevik MO, Bozgeyik I, Aksoy AF, Bağış H, Arslan A. 2015. Cell viability, anti-proliferation and antioxidant activities of Sideritis syriaca, Tanacetum argenteum sub sp. argenteum and Achillea aleppica subsp. zederbaueri on human breast cancer cell line (MCF-7). J Appl Pharm Sci. 5: 001-005.

Yumrutaş Ö, Pehlivan M, Güven C, Bozgeyik I, Bozgeyik E, Yumrutas P,Temiz E, Üçkardeş F. (2018). Investigation of cytotoxic effect of salvia pilifera extracts and synthetic chlorogenic and caffeic acids on DU145 prostate cancer cells line. KSÜ Doğa Bilimleri Dergisi. 21:141-147.

Zhao BX, Sun YB, Wang SQ, Dua L, Huo QL, Ren F, Li GF. 2013. Grape seed procyanidin reversal of p-glycoprotein associated multi-drug resistance via down-regulation of NF-κB and MAPK/ERK mediated YB-1 activity in A2780/T cells. PloS ONE. 8: e71071.