REVIEW ARTICLE

RECENT ADVANCES TOWARDS THE SYNTHESIS OF CHRYSIN DERIVATIVES HAVING ANTI-CANCER ACTIVITIES

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ARTICLE INFO	ABSTRACT
	Chrysin is a potential natural flavonoid that exhibited a broad spectrum of biological activities including antioxidant, anticancer, antiviral, anti-hypertension, anti-inflammatory and antidiabetic properties. Due to its poor solubility in the common polar solvents like water, its application in drug discovery is limited. Recently, researchers have paid efforts towards the synthesis of chrysin-analogs and conjugates with improved efficacy and selectivity, for developing more active chrysin-based molecules for the clinical test. As a result, many semi-synthetic chyrsin derivatives have been developed that exhibited several therapeutic activities with better efficiency and solubility. In this review, the recent developments towards the design and synthesis of chrysin derivatives, and their applications in the biological science as anticancer agents have been discussed.

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INTRODUCTION

Flavonoids are omnipresent naturally occurring polyphenolic compounds that are commonly found in fruits and vegetables,[1] exhibiting several therapeutic activities, and the most important activity is their potential role as anticancer agents.[2] Chemically flavonoids are the low-molecular weight compounds, including flavanones, anthocyanidins, flavonols, flavanols, isoflavones, dihydroflavonols, and flavones.[3-5] All the flavonoids compounds contain benzo-γ—pyrone basic skeleton with poly hydroxyl groups.[6,7] Flavones are the subgroups of flavonoids and considered as a secondary metabolite of plants. They are widely distributed in plant tissues.[8] In plants flavone combine with sugar via free hydroxyl groups and share common structural features: the C6-C3-C6 sequence of the carbon skeleton.[9] Several flavones such as chrysin, luteolin, and apigenin, displayed a broad spectrum of biological activities and widely used in traditional Chinese medicine.[10] Among these, chrysin is one of the most important natural flavone that exhibited a variety of pharmaceutical properties. Chemically, chrysin is 5,7-dihydroxyflavone, commonly found in many plants extracts. It has been used as a potential chemotherapeutic and natural agent with various biological activities including anticancer,[11] anti-inflammatory,[12] antioxidant,[13] antibacterial,[14] anti-diabetic,[15] anxiolytic,[16] and hepatoprotective[17] activities. Several groups investigated the potential clinical applications of chrysin derivatives.

For example, Dhawan and co-workers described the applications of chrysin against physiological and biochemical effects of aging.[18] Kim and co-workers[19] first observed that chrysin could down regulate melanogenesis. They suggested that chrysin could be useful as skin hyperpigmentation therapeutic agent. In Chinese and other Asian countries, chrysin is used as herbal folk-medicine. Recently, in-silico investigation revealed that chrysin derivatives are also effective against SARS-CoV-2 virus proteins.[20] Due to its high biological activities, the in-vitro investigation with chrysin derivatives for various health benefits has been increased nowadays. But, the potential applications of chrysin have been reduced significantly due to its poor solubility, small intestinal absorption and the rapid metabolism of glycosylation. Researchers assume that modifications of chrysin nucleus with different functionalities may be improved the solubility and absorption, and hence, will enhanced the biological functions of chrysin derivatives. Bioavailability is also a vital issue in view of potential biological effects *in vivo*. The bioavailability studies of chrysin revealed that most of the absorbed chrysin molecule was detected in the blood stream and vascular system as glucuronic acid and sulfate acid conjugates due to unprotected hydroxyl at 5 and 7 positions of chrysin.[21] Of late, huge efforts had been made on designing and synthesis of its analogs and conjugates to obtain molecules with improved efficacy and selectivity.[22] In this article, the recent advances towards the design, synthesis and ani-cancer activities of chrysin derivatives have been discussed.

Anticancer activity of chrysin derivatives: In 2004, Woo and co-workers[23] investigated the effect of chrysin on the apoptotic pathway in U937 human promonocytic cells. They observed that chrysin have potential to induce apoptosis of cultured cancer cells without destroying normal cells through caspase activation and Akt inactivation in U937 leukemia cells. Overexpression of a constitutively active myr-Akt in U937 cells inhibited the induction of apoptosis, activation of caspase 3, and PLC-gamma1 cleavage by chrysin. In 2007, Fu *et al*. investigated the mechanism through which chrysin inhibits the growth of cancer cells.[24] The authors observed that the anticancer activity of chrysin was mediated by inhibiting hypoxia-inducible factor-1alpha and vascular endothelial growth factor in human prostate cancer DU145 cells. Later on, Sun *et al*.[25] and Sawicka *et al*.[26] independently investigated the anticancer activities of chrysin. Sun *et al* observed that chrysin exhibited anticancer activity by inhibition of histone deacetylase enzymatic activity; whereas Sawicka *et al*. reported that the antiproliferative effects of chrysin in cancer cells are the result of the suppression of complexes of cyclins, as well as cell cycle arrest. These results indicated that natural chrysin could be an effective chemoprevention and cancer therapeutics agent.

Anticancer activity of semi-synthetic chrysin derivatives: Due to the poor bioavailability of chrysin, many researchers have paid attention for the development of novel chrysin derivatives with high efficacy, low toxicity, and minimum side effects. In this regard, Zheng and co-workers[27] prepared a few halogen derivatives of chrysin to evaluate the anticancer activities against human gastric adenocarcinoma cell line SGC-7901 and colorectal adenocarcinoma cell line HT-29. The authors observed that 8-bromo-5-hydroxy-7-methoxy chrysin showed the most potent activity against HT-29 with a IC50 value 2.2 lg/mL, while 5,7-dimethoxy-8-iodochrysin showed the strongest activity against SGC-7901 (IC50 = 1.9 lg/mL) (Figure 1). These results indicated that halo-substituted chrysin derivatives showed the better anti-tumar activities than natural chrysin molecule. Later on, scientists have synthesized several chrysin derivatives having strong electronegative group at either C3 or C8 positions which promote lipophilicity, and the anticancer activity of chrysin.

In this regard, Zheng *et al*.[28] synthesized thirteen chrysin derivatives with an aim to investigate the role of halogen functional groups and to discover more potential chrysin-based molecules having anticancer activity.The authors carried out the *in vitro* evaluation of anticancer activities of the synthesized compounds against SGC-7901, HT-29, and human promyelocyticleukemia cell line HL-60. Zheng *et al*. observed that 5,7-dimethoxy-3'-trifluoromethyl chrysin having a strong electron-withdrawing group (CF_3) at 3'-position of B ring of chrysin nucleus showed higher anticancer activity than 5-fluorouracil. From this observation, the authors assumed that halo-groups such as CF_3 may be considered as a key pharmacophore for enhanced anti-tumor activity. The authors also assumed that introduction of strongly electronegative group at either C-8 or C-3-position may elevate the lipophilicity as well as the anticancer activity of chrysin. Zhu and co-workers[29] synthesized a series of 5,7-disubstituted chrysin, 7-mono-substituted chrysin, 5-monosubstituted chrysin derivatives by alkylation, acetylation, benzoylation, carboxymethylation, and evaluated the antitumor activity against H22 cells. In 2009, Li and co-workers[29] found that bromochrysins derivatives are active against HL-60 and HT-29 tumor cells. Wei *et al*. observed that iodo-chrysin derivatives are active against SW-579 tumor cells.[30] To improve the potency and physiochemical properties of chrysin, in 2017 Wang *et al*.have synthesized a series of fluorine-substituted chrysin derivative and evaluated their proliferation activity against HepG2 cells.[31] Recent studies on fluorinated chrysin derivatives revealed that the chrysin compounds containing fluorine atom were active against A549, HepG2, HCMV and SGC-7901 cells.[33] This indicated that the fluorine substitution improve the anti-cancer activity of chrysin due to strong electronegative properties. In another work, Bianand co-workers[32] modified the chrysin nucleus by introducing a piperazine group and found an increased inhibitory activity against A549 and HepG2 cells. Scientists have been found that epidermal growth factor receptor (EGFR) kinase closely correlated with cancer.

Overexpression of EGFR was found in many tumor cells. Lv and co-workers [34] synthesized twenty chrysin derivatives having long-chain
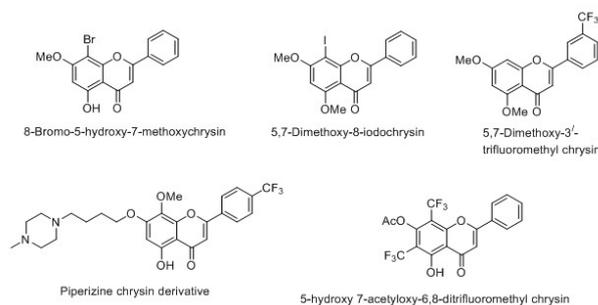

8-Bromo-5-hydroxy-7-methoxychrysin

5,7-Dimethoxy-8-iodochrysin

5,7-Dimethoxy-3'-trifluoromethyl chrysin

Piperizine chrysin derivative

5-hydroxy 7-acetyloxy-6,8-ditrifluoromethyl chrysin

Figure 1. Important halo derivatives of chrysin active against cancer cells

alkyl groups and investigated the inhibitory activities against EGFR, and antiproliferative activities against HT-29 cell. By analyzing the structure activity relationships (SAR) of the synthetic compounds, the authors also found that the inhibitory activities of these chrysin derivatives were increasing with increase in the number of long-chain carbon atoms up to 16 carbons. But the activity was not increasing further when the number of carbon atoms was more than 16. The authors observed that the chrysin derivatives exhibited highest inhibitory activities against antiproliferative (IC50 = 0.87 and 4.2 lg/mL, respectively) and EGFR kinase (IC50 = 0.048 and 0.035 lg/mL, respectively). These two molecules may be considered as potential anticancer agents. Kalibaba co-workers also observed that EGFR signaling pathway is a prominent target for anticancer therapy.[35] Very recently, Debnath and co-workers synthesized a few C-7 hydroxyyproton-substituted chrysin-based EGFR inhibitors and suggested the two chrysin based compounds as EGFR inhibitors for breast cancer (Figure 2).[36]
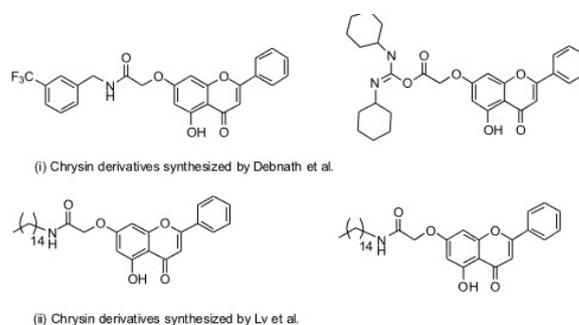

(i) Chrysin derivatives synthesized by Debnath et al.

(ii) Chrysin derivatives synthesized by Lv et al.

Figure 2. Some important long-chain alkyl groups containing chrysin derivatives

Recently, Hu *et al*. analysed the structure activity relationships (SAR) of chrysin derivatives and found that long chain carbon atom can increase the anti-cancer activities of chrysins.[37] The authors prepared a series of novel chrysin derivatives, in which C-7-OH group of chrysin has been linked with different hydrophilic amines separated by two carbon spaces. The authors found that 7-(2-(piperazin-1-yl)ethoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (Figure 3) showed the strongest activity against human colon cancer cell line HCT-116, human cervical carcinoma cell line Hela, human prostate cell line DU-145, human leukemia cell line K562, and SGC-7901. The authors assumed that piperazin-1-yl ethoxy group of compound may be an important motif responsible for the highest potency against cancer cells. Low toxicity and favorable water solubility of this molecule, makes it a very promising antitumor drug candidate. These preliminary results clarified that introduction of nitrogen-containing polar groups into chrysin molecule indeed enhanced its anticancer activity. Later on, in 2018, Gourav *et al*.,[38] observed that long carbon chain on chrysin have maximum incorporation and drug loading capacity due to its enhanced hydrophobocity. They carry out a comparative study with chrysin derivatives having different carbon chain against anticancer activity of human neuroblastoma cell lines

with nanostructure lipid carriers. Recently, Suresh *et al.* performed the molecular docking study of some natural flavonoid chrysin derivatives for the anticancer activity using Molegro Virtual Docker (MVD) software.[39] Sergio *et al* have synthesized a few fluorinated Se-chrysin that exhibited better anti-A549 cell activity. The author observed that semi-synthetic compound, 6,8-bis(o-tolylselanyl)-chrysin showed the most potent antioxidant activity (Figure 3).[40]
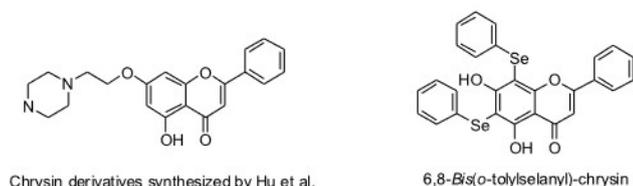

Chrysin derivatives synthesized by Hu et al.

6,8-*Bis*(o-tolylselanyl)-chrysin

Figure 3. Chrysin derivatives containing piperazin and selenium atom

CONCLUSION

In this review, the recent progresses towards the synthesis of chrysin derivatives and their potential biological applications as anti-cancer agents have been discussed. There is no doubt that chrysin is a biological active molecule, like many other secondary metabolites. It has been considered as a hot spot for the development of potential chemopreventive agent. This review summarises the considerable synthetic effort made toward ''better chrysin derivatives'' with greater solubility''. Bioactivity of the synthesized chrysin derivatives seems to indicate ample space for designing new drugs for clinic.

Conflicts of Interest: The author declared that there is no conflict of interest.

REFERENCES

1. Scalbert, A, Williamson, G. (2000). Dietary intake and bioavailability of polyphenols. *J. Nutr.* 130, 2073–2085.
2. (a) Zhang S, Wang X, Sagawa K, Morris ME (2005) Flavonoids chrysin and benzoflavone, potent breast cancer resistance protein inhibitors, have no significant effect on topotecan pharmacokinetics in rats or mdr1a/1b (-/-) mice. *Drug MetabDispos* 33:341–348. doi:10.1124/dmd.104.002501. (b) De Souza Dos Santos MC, Gonc¸alves CF, Vaisman M, Ferreira AC, de Carvalho DP (2011). Impact of flavonoids on thyroid function. *Food ChemToxicol* 49:2495–2502. doi:10.1016/j.fct.2011.06. 074. (c) Liu HL, Jiang WB, Xie MX. (2010). Flavonoids: recent advances as anticancer drugs. *Recent Pat Anticancer Drug Discov.* 5(2), 152-64. doi: 10.2174/157489210790936261.
3. Beecher, G.R. (2003). Overview of Dietary Flavonoids: Nomenclature, Occurrence and Intake. *J. Nutr.* 133, 3248–3254.
4. Hodnick, W.F.; MllosavljeviC, E.B.; Nelson, J.H.; Pardini, R.S. (1988). Electrochemistry of flavonoids: Relationships ´ between redox potentials, inhibition of mitochondrial respiration, and production of oxygen radicals by flavonoids. *Biochem. Pharmacol.*37, 2607–2611.
5. Namdeo, A.G.; Boddu, S.H.; Amawi, H.; Ashby, C.R., Jr.; Tukaramrao, D.B.; Trivedi, P.; Tiwari, A.K. (2020). Flavonoids as Multi-Target Compounds: A Special Emphasis on their Potential as Chemo-adjuvants in Cancer Therapy. *Curr. Pharm. Des.* 26, 1712–1728.
6. Scalbert A, Williamson G (2000). Dietary intake and bioavailability of polyphenols. *J Nutr* 130, 2073S–2085S
7. Suyenaga ES, Konrath EL, Dresch RR, Apel MA, Zuanazzi JA, Chaves CG, Henriques AT (2011). Appraisal of the antichemotactic activity of flavonoids on polymorphonuclear neutrophils. *Planta Med* 77:698–704. doi:10.1055/s-0030-1250516
8. Martens S, Mitho¨fer A (2005). Flavones and flavone synthases. *Phytochemistry* 66:2399–2407. doi:10.1016/j.phytochem.2005.07.01
9. Bojic´ M, Debeljak Z, Tomic˘ic´ M, Medic´-S˘aric´ M, Tomic´ S (2011). Evaluation of antiaggregatory activity of flavonoid aglycone series. *Nutr J.* doi:10.1186/1475-2891-10-73
10. (a) Wenzel U, Kuntz S, Brendel MD, Daniel H (2000). Dietary flavone is a potent apoptosis inducer in human colon carcinoma cells. *Cancer Res* 60:3823–3831. (b) Leonard E, Yan Y, Lim KH, Koffas MA (2005). Investigation of two distinct flavone synthases for plant-specific flavone biosynthesis in Saccharomyces cerevisiae. *Appl Environ Microbiol* 71:8241–8248. doi:10.1128/AEM.71.12.8241-8248. 2005
11. (a) Khoo BY, Chua SL, Balaram P (2010). Apoptotic effects of chrysin in human cancer cell lines. *Int J MolSci* 11:2188–2199. doi:10. 3390/ijms11052188. (b) Pick A, Mu¨ller H, Mayer R, Haenisch B, Pajeva IK, Weigt M, Bo¨nisch H, Mu¨ller CE, Wiese M (2011). Structure-activity relationships of flavonoids as inhibitors of breast cancer resistance protein (BCRP). *Bioorg Med Chem* 19:2090–2102. doi:10.1016/j.bmc.2010.12.043
12. (a) Shin EK, Kwon HS, Kim YH, Shin HK, Kim JK (2009).Chrysin, a natural flavone, improves murine inflammatory bowel diseases. *BiochemBiophys Res Commun* 381:502–507. doi:10.1016/j. bbrc.2009.02.071. (b) Gresa-Arribas N, Serratosa J, Saura J, Sola` C (2010). Inhibition of CCAAT/enhancer binding protein d expression by chrysin in microglial cells results in anti-inflammatory and neuroprotective effects. *J Neurochem* 115:526–536. doi:10.1111/j.1471-4159. 2010.06952.x
13. (a) Bajgai SP, Prachyawarakorn V, Mahidol C, Ruchirawat S, Kittakoop P. (2011). Hybrid flavan-chalcones, aromatase and lipoxygenase inhibitors, from Desmoscochinchinensis. *Phytochemistry* 72:2062–2067. doi:10.1016/j.phytochem.2011.07.002 (b) Chen YH, Yang ZS, Wen CC, Chang YS, Wang BC, Hsiao CA, Shih TL (2012). Evaluation of the structure-activity relationship of flavonoids as antioxidants and toxicants of zebrafish larvae. *Food Chem*134:717–724. doi:10.1016/j.foodchem.2012.02.166
14. Wang J, Qiu J, Dong J, Li H, Luo M, Dai X, Zhang Y, Leng B, Niu X, Zhao S, Deng X (2011). Chrysin protects mice from Staphylococcus aureus pneumonia. J *ApplMicrobiol* 111:1551–1558. doi:10.1111/j.1365-2672.2011.05170.x
15. (a) Lukacinova A, Mojzis J, Benacka R, Keller J, Maguth T, Kurila P, Vasko L, Racz O, Nistiar F (2008). Preventive effects of flavonoids on alloxan-induced diabetes mellitus in rats. *Acta Vet Brno* 77:175–182. doi:10.2754/avb200877020175 (b) Torres-Piedra M, Ortiz-Andrade R, Villalobos-Molina R, Singh N, Medina-Franco JL, Webster SP, Binnie M, Navarrete-Va´zquez G, Estrada-Soto S (2010). A comparative study of flavonoid analogues on streptozotocin-nicotinamide induced diabetic rats: quercetin as a potential antidiabetic agent acting via 11betahydroxysteroid dehydrogenase type 1 inhibition. *Eur J Med Chem* 45:2606–2612. doi:10.1016/j.ejmech.2010.02.049
16. (a) Zanoli P, Avallone R, Baraldi M (2000). Behavioral characterisation of the flavonoids apigenin and chrysin. *Fitoterapia* 71(1):S117– S123. doi:10.1016/S0367-326X(00)00186-6; (b) Brown E', Hurd NS, McCall S, Ceremuga TE (2007). Evaluation of the anxiolytic effects of chrysin, a Passifloraincarnata extract, in the laboratory rat. AANA J 75:333–337
17. Pushpavalli G, Kalaiarasi P, Veeramani C, Pugalendi KV (2010). Effect of chrysin on hepatoprotective and antioxidant status in Dgalactosamine-induced hepatitis in rats. *Eur J Pharmacol* 631:36–41. doi:10.1016/j.ejphar.2009.12.031
18. Dhawan K, Kumar S, Sharma A (2002). Beneficial effects of chrysin and benzoflavone on virility in 2-year-old male rats. *J Med Food* 5:43–48
19. Kim DC, Rho SH, Shin JC, Park HH, Kim D (2011). Inhibition of melanogenesis by 5,7-dihydroxyflavone (chrysin) via

blocking adenylyl cyclase activity. *BiochemBiophys Res Commun*411:121–125. doi:10.1016/j.bbrc.2011.06.108

20. Basu A, Sarkar A, Maulik, U. (2020). Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2. *Sci Rep* 10, 17699. https://doi.org/10.1038/s41598-020-74715-4

21. (a) Walle UK, Galijatovic A, Walle T (1999) Transport of the flavonoid chrysin and its conjugated metabolites by the human intestinal cell line Caco-2. *BiochemPharmacol* 58:431–438. doi:10.1016/ S0006-2952(99)00133-1; (b) Tsuji PA, Winn RN, Walle T (2006). Accumulation and metabolism of the anticancer flavonoid 5,7-dimethoxyflavone compared to its unmethylated analog chrysin in the Atlantic killifish. *ChemBiol Interact* 164:85–92. doi:10.1016/j.cbi. 2006.08.023

22. Liu Y, Xiudao Song, Jun He, Xing Zheng and Houlv Wu. (2014). Synthetic derivatives of chrysin and their biological activities. *Med Chem Res* 23:555-563.

23. Woo KJ, Jeong YJ, Park JW, Kwon TK (2004).Chrysin-induced apoptosis is mediated through caspase activation and Akt inactivation in U937 leukemia cells. *BiochemBiophys Res Commun* 325:1215–1222. doi:10.1016/j.bbrc.2004.09.225

24. Fu B, Xue J, Li Z, Shi X, Jiang BH, Fang J (2007).Chrysin inhibits expression of hypoxia-inducible factor-1alpha through reducing hypoxia-inducible factor-1alpha stability and inhibiting its protein synthesis. *Mol Cancer Ther* 6:220–226. doi:10.1158/ 1535-7163.MCT-06-0526

25. Sun LP, Chen AL, Hung HC, Chien YH, Huang JS, Huang CY, Chen YW, Chen CN (2012).Chrysin: a histone deacetylase 8 inhibitor with anticancer activity and a suitable candidate for the standardization of Chinese propolis. *J Agric Food Chem* 60: 11748–11758. doi:10.1021/jf303261r

26. Sawicka D, Car H, Borawska MH, Niklin´ski J (2012). The anticancer activity of propolis. *Folia HistochemCytobiol* 50:25–37. doi:10. 2478/18693

27. Zheng X, Meng WD, Xu YY, Cao JG, Qing FL (2003) Synthesis and anticancer effect of chrysin derivatives. *Bioorg Med ChemLett* 13:881–884. doi:10.1016/S0960-894X(02)01081-8

28. Zheng X, Zhao FF, Liu YM, Yao X, Zheng ZT, Luo X, Liao DF (2010). Synthesis and preliminary biological evaluation of chrysin derivatives as potential anticancer drugs. *Med Chem* 6:6–8. doi:10.2174/157340610791208763

29. Zhu ZY, Wang WX, Wang ZQ, Chen LJ, Zhang JY, Liu XC, Wu SP, Zhang YM. (2014). Synthesis and antitumor activity evaluation of chrysin derivatives. *Eur J Med Chem*. 75, 297-300. doi: 10.1016/j.ejmech.

30. Wei Y, Zheng Q, Tang G. (2016). Synthesis and anti-thyroid cancer effect of iodo-chrysin derivatives. *Med Chem*. 12(5):441-447.

31. Wang J, Ge R, Qiu X. (2017). Discovery and synthesis of novalWogonin derivatives with potent antitumor activity in vitro. *Eur. J. Med. Chem*.140:421-434.

32. BianJ, Li T,Weng T, Wang J, Chen Y, Li Z. (2017). Synthesis evaluation and quantitative structure-activity relationship (QSAR) analysis of wogonin derivatives as cytototic agents. *Bioorg Med ChemLett*. 27 (4):1012-1016.

33. Zhu Y, Yao X, Long J, Li R, Liu Y, Yang ZH, Zheng X. (2019). Flourine- containing chrysin derivatives: Synthesis and biological activity. *Natur Product Communin*. 14 (9):1-11.

34. Lv PC, Wang KR, Li QS, Chen J, Sun J, Zhu HL (2010). Design, synthesis and biological evaluation of chrysin long-chain derivatives as potential anticancer agents. *Bioorg Med Chem* 18:1117–1123. doi:10.1016/j.bmc.2009.12.048

35. Kalibaba KS and Druker BJ.(1997). Protein tyrosine kinase and cancer. *BiochimBiophysActa*. 1333:217-248.

36. Sudhan D, Manupati K, Minarul I, Ragini Y, Debanjan S, Amitava D. (2019). *In silico*Design, Synthesis and Activity of Potential Drug-like Chrysin Scaffold-derived Selective EGFR Inhibitors as Anticancer Agents. *ComputBiol Chem*. 83:107156. doi: 10.1016/j.compbiolchem.2019.107156.

37. Hu K, Wang W, Cheng H, Pan SS, Ren J (2011). Synthesis and cytotoxicity of novel chrysin derivatives. *Med Chem Res* 20:838–846. doi:10.1007/s00044-010-9395-1

38. Gourav K, Prasant N, Priyam C, Biplab R, Pritam G, Koji T,KanjiraoT,Annop K. (2018). Physicochemical characterization of chrysin derivative loaded nanostructured lipid carriers with special reference to anticancer activity.*J SurfacDetergen*. 21(3), 421-432.

39. Suresh CD and Sudha V. (2017). Docking study of chrysin derivatives on different targets for anticancer activity. *J Drug Deliv & Therapeu*. 7(7):131-133.

40. Fonseca SF, Padilha NB, Thurow S, *et al*. (2017). Ultrasound-promoted copper-catalyzed synthesis of bis-arylselanylchrysin derivatives with boosted antioxidant and anticancer activities. *Ultrason Sonochem*. 39, 827-836.

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