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REVIEW ARTICLE

Anti-cancer Activity of Chrysin in Cancer Therapy: a Systematic Review

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Abstract

Chrysin is a natural bioactive compound that is extracted from many trees, honey, and propolis. Chrysin has several pharmacological activities such as anti-inflammatory, anti-cancer, and antioxidant properties. This study was performed to evaluate the anti-cancer activities of chrysin in cancer therapy. The present study was conducted by systematic review of studies published up to August 2021. Related studies were identified by searching Web of Science (WoS), PubMed, Science Direct, SID, MagIran, Scopus, and Google Scholar databases. The keywords of chrysin, cancer, anti-cancer, and cancer therapy were used for searching. The quality of the studies was assessed by the CONSORT checklist. A total of 21 studies were identified. The results of studies showed that chrysin has an anticancer effect by stimulating apoptosis in a wide range of human cells and rats. Chrysin is also an important factor in inhibiting tumor growth and neoplasticity. Chrysin inhibits the growth and proliferation of cancer cells by inducing cytotoxic effects. Therefore, due to the antitumor effects of chrysin and its safety and non-toxicity towards normal cells, this compound can be considered as an adjuvant along with chemotherapeutic agents in cancer treatment.

Keywords Chrysin · Anti-cancer · Cancer therapy · A systematic review

Background

Cancer is the result of cells deviating from normal regulatory, proliferative, and differentiation pathways. Self-efficacy in growth signals, insensitivity to growth inhibitory signals, avoidance of programmed cell death, and having unlimited potentials for metastasis lead to cell immortality and cancer (1). Cancer is responsible for 1 in 8 deaths worldwide and encompasses more than 100 distinct diseases with different epidemiology and risk factors (1, 2). Annually, nine million new cases of cancer are identified in developed and developing countries (3). It has been predicted that in 2030,

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cancer will be the first and most important cause of human death (4).

Common cancer treatments include surgical tumor resection, chemotherapy, and radiotherapy (5). Natural products, especially herbs, have been used to treat many diseases, including cancer, for many years. Studies show that there are more than 3000 types of plants used to treat cancer (6). Foods rich in antioxidants have inhibitory effects on cancers, inflammatory diseases, and dementia. Honey is one of these foods (7, 8), which has long been used for its antioxidant properties. Chrysin, as one of the polyphenols of honey, has shown promising pharmacological effects for the prevention and treatment of cancer (9). Additionally, propolis, passion flowers, *Passiflora caerulea*, *P. incarnata*, and *Oroxylum inolicum* are among rich sources of chrysin (10, 11) (Fig. 1).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs. The beneficial effects of NSAIDs in reducing or relieving pain are well established, and other benefits such as reducing inflammation and anti-cancer effects are also documented. NSAIDs have been shown to induce reactive oxygen species (ROS) in different cell types including cardiac and cardiovascular-related cells. Increases in ROS result in increased levels of oxidized proteins which alter key intracellular signaling pathways (11).

Chrysin (5,7-dihydroxyflavone) (C15H10O4) is a natural flavonoid found in honey and a variety of plant extracts (12). Chrysin has several biological activities, such as antioxidant (13), anti-inflammatory (14), antibacterial (15), anti-hypertensive (16), anti-allergic (17), vasodilator (18), anti-diabetic (19), anti-anxiety (10), anti-viral (20), anti-estrogen (21), liver protective (22), anti-aging (23), anti-seizure (24), and anti-cancer effects (25). Although the exact molecular mechanisms of the anti-cancer effects of chrysin are not fully understood, it seems that this compound induces apoptosis in cancer cells in the following mechanisms: (1) facilitating the release of cytochrome C from the mitochondria, (2) activating caspase-3 and inhibiting the activity of the XIAP molecule, and (3) reducing AKT phosphorylation and triggering the PI3K pathway and induction of apoptosis (26).

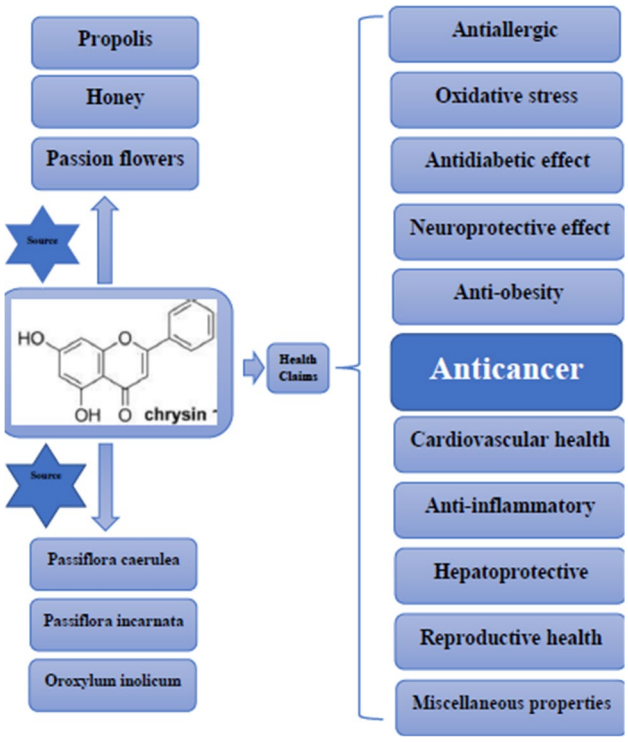

Fig. 1 Schematic of chrysin sources and its health claims

In a study by Rauf et al., it was reported that chrysin has recently attracted attention for its anti-tumor and anti-oxidant activities and also for its protective effects on allergic inflammation (27). This study reports that in silico analysis of receptor-ligand complex shows that chrysin interacts weakly with COX-1 binding site whereas displayed a remarkable interaction with COX-2. These findings suggest that the flavone chrysin is isolated from *P. evestita* Th. Wolf. and possesses in vivo anti-inflammatory and anti-nociceptive potential, which is supported in silico by interaction with the COX-2 binding site (27).

Great advances have been made in understanding the molecular biology of cancer, leading to breakthrough developments in anti-cancer therapies. Several studies have suggested an association between dietary phytochemicals and cancer prevention (27–29). Experimental evidences show that many phytochemicals have anticancer activity with low toxicity, thus making them safe for human use. Chrysin administration improves status on lipid peroxidation and antioxidants, which regulates the oxidant/antioxidant balance in cancer (30). The main anti-cancer mechanisms of chrysin include suppressing cellular proliferation and inflammation and inducing apoptotic cell death (31, 32). Chrysin can also be an effective inhibitor of tumor cell–induced angiogenesis. Chrysin also delays tumor formation instead of inhibiting tumor formation (33).

Nowadays, cancer studies are looking for effective and safe anti-tumor agents with greater acceptability. Natural products, such as plant-derived compounds that are either traditional herbal medicines or parts of the human diet, have attracted attention in this field. Numerous studies have confirmed the efficiency of these natural products as anti-cancer agents in various experimental models of human cancers (34–39), and a small number of compounds are subjected to clinical trials (11) (Fig. 1).

Natural products are a promising source for discovering new anti-cancer drugs. In the current review, we conducted a systematic review on the anti-cancer effects of chrysin. Therefore, a systematic review of all studies in this field and their combination can create a more complete picture on the potential capacity of chrysin as an anti-cancer agent.

Methods

Search Strategy

The present study was conducted by a systematic review of studies published up to August 2021 and examined the anti-cancer activity of chrysin in cancer therapy. The Preferred Reporting Items for Systematic Review and Meta-Analyses statement (PRISMA) checklist was used in all stages of this systematic review (40). The databases such as PubMed, Scopus, Science direct, Magiran, SID, WoS, and Google Scholar were reviewed to identify studies published in Persian and English languages. For this purpose, the keywords of chrysin, anti-cancer, cancer therapy, and their combinations were used for literature search by two independent researchers. Also, the reference list of articles was reviewed to find potential additional studies. The title and abstract of the articles were screened according to search strategy, and after the articles were approved in terms of the topic, the full text of articles was reviewed by two researchers independently.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) studies that examined the anti-cancer properties of chrysin, (2) interventional studies, (3) studies with full text available, (4) studies focused on cancer and chrysin, (5) clinical trials published in English and Persian. The exclusion criteria were (1) studies focused on other compounds, (2) studies that lacked sufficient detail in method, (3) reviewed articles, (4) letters to the editor, (5) papers presented at conferences, (6) conference abstracts, and (7) non-English articles.

Quality Assessment

In order to assess the quality of articles, a checklist appropriate to the type of study was used. The 2010 CONSORT (Consolidated Standards of Reporting Trials) was used to review standard reporting (41). This checklist contains 25 checkpoints resulting in a possible range of 0–25. Thus, the maximum score was 25 points. For each article, all checklist items were reviewed by two researchers, and articles of good quality were included in the study.

Data Extraction

Information on all articles submitted to the systematic review process was extracted using a pre-prepared checklist. This checklist includes the first author's name, the year of publication, the place of study, the duration of the study, the dose of the drug, the type of cancer, the sample size, the examined outcomes, and the main findings.

Results

Study Characteristics

A total of 1304 studies were identified by the initial search in 7 electronic databases and transferred into the reference management software (Fig. 2). After removing duplicate articles and irrelevant articles ($n=705$), the title and abstract of 599 articles were reviewed according to the inclusion and exclusion criteria. A total of 287 articles were selected for full-text assessment, and 22 articles remained after reviewing the full-text articles. The methodological quality of 22 articles was assessed using the CONSORT checklist. Finally, 21 articles were included in this study to evaluate the anti-cancer activity of chrysin. The characteristics of included studies are shown in Table 1.

In general, all of the included studies were controlled trials. This systematic review was performed on in vitro and in vivo studies. A total of 21 studies, 8 studies in China (43) (33, 57) (56), 4 studies in Korea (42, 48, 53, 55), 4 studies in India (30) (45, 49, 50), and 2 studies in the USA (46) (35), were conducted. In Iran (54), Thailand (44), and Japan (52), one study was conducted. The duration of studies ranged from 16 to 16 weeks.

The included studies contained eleven types of cancers, including lung cancer ($n=5$) (45) (46) (34) (48) (52), breast cancer ($n=3$) (43) (44) (56), colorectal cancer ($n=4$) (54, 55) (47) (51), renal cancer ($n=2$) (33) (49), thyroid cancer (35), skin cancer (42), hepatocellular carcinoma (50), oral cancer (30), esophagus cancer (57),cervical cancer (58), and gastric cancer (53). RNA extraction has been performed in all studies in this systematic review. Protein analysis was also performed by real-time PCR, Western blot, and ELISA methods.

According to the results of this systematic review, chrysin is a compound with anti-inflammatory and antioxidant effects. Chrysin has also been shown to have anti-cancer effect by stimulating apoptosis in a wide range of human and rat cells. However, there is still ambiguity in the anti-cancer mechanisms of chrysin. Chrysin is also an important factor in inhibiting tumor growth and neoplasticity and delaying tumor development.

Discussion

This systematic review included 21 studies and focused on the anti-cancer activities of chrysin. All studies had moderate or high quality according to the CONSORT checklist.

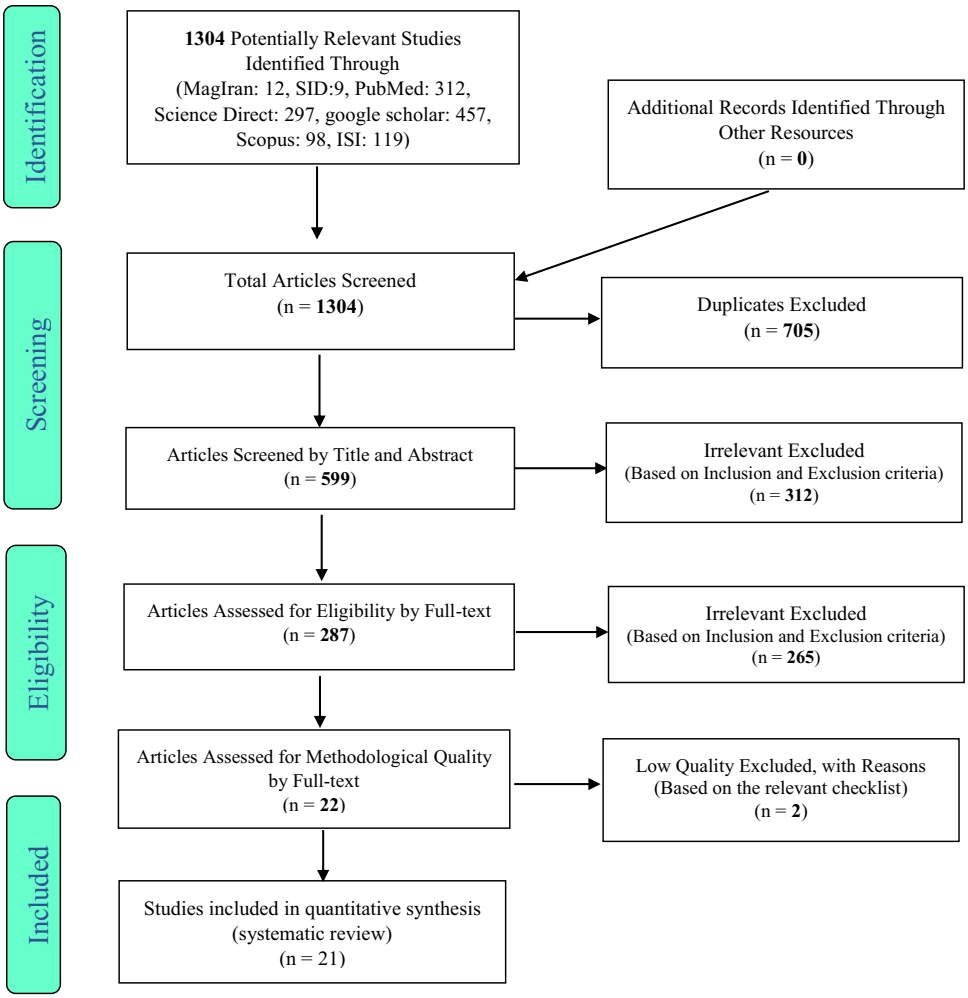

Fig. 2 Flow chart indicating the stages of article selection in this systematic review and meta-analysis (PRISMA 2009)

To our knowledge, this study is the first systematic review to summarize anti-cancer activities of chrysin. According to the studies, chrysin promotes growth inhibitory effects against human cancer cell lines and tumors via suppressing cellular proliferation and inducing apoptosis. These effects can be mediated through a variety of cellular and molecular mechanisms affected by chrysin.

Using natural products as complementary to chemotherapeutic agents leads to sensitizing cancer cells to chemotherapeutic agents (59, 60). Antitumor phytochemicals can suppress the proliferation, metastasis, and invasive behaviors of cancer cells (61–63). Flavonoids are present in fruits, plant-derived extracts, and many dietary supplements or herbal medicines. Chrysin is a natural, non-toxic, and safe flavonoid in propolis, which has shown strong anti-cancer effects on tumor cells (58). Chrysin induces apoptosis through the intrinsic mitochondrial pathway that disrupts mitochondrial membrane potential (MMP) and increases DNA fragmentation. It also produces pro-apoptotic proteins, including Bax and Bak, and activates caspase-9 and caspase-3 in various cancer cells (31, 64). In addition, chrysin can inhibit tumor growth by activating P38 MAPK and stopping the cell cycle (65). Regarding the high antitumor activity of chrysin, this natural plant-derived compound can be beneficial in inhibiting chemotherapy resistance of cancer cells (66). Also, chrysin suppresses tumorigenesis by inhibiting histone deacetylase 8 (HDAC8) (67).

Zhang et al. showed that chrysin suppressed the proliferation of HeLa cells and induced apoptosis. Their result showed that chrysin has cytotoxic effects on esophageal squamous cell carcinoma cell line (KYSE-510) in a dose- and time-dependent manner (58). Khan and colleagues also reported that chrysin (250 mg/kg) can suppress N-nitrosodiethylamine-induced preneoplastic nodules in male Wistar rats (50). These authors showed in another study that dimethyl chrysin can attenuate Wnt and NF-κB signaling pathways and modulate apoptotic gene expression in DEN-induced primary hepatocarcinogenesis in male Wistar rats (68).

In xenograft models, chrysin can inhibit angiogenesis and inducing apoptosis in HTh7 cells, 4T1 mice, and MDA-MB-231 cells (34, 37, 43, 66). Kasala et al. also concluded

Table 1 Characteristics of included articles in the systematic review

Author	Year	Region	Type of cancer	Sample	Duration of study	Dosage of the drug	Animal model/cell line	Phase	Main results
Karthikeyan et al. (30)	2013	India	Oral	24	14 weeks	250 mg/kg b.w	Male golden Syrian hamsters	I and II	Chrysin has the potential to delay rather than inhibit tumor formation
Yu et al. (35)	2013	USA	Thyroid	18	3 weeks	75 mg/kg b.w 25, 50 & 75 µM/ml	Male nude mice HTh7; KAT18 cell lines¶	NA	Chrysin inhibits tumor growth in ATC both in vitro and in vivo
Liu et al. (42)	2013	Korea	Skin	18	1 weeks	10 µM	JB6 P	G0/G1, S, or G2/M	Chrysin is an effective agent for inhibiting neoplastic transformation and tumor growth
Yang et al. (43)	2014	China	Breast	15	NA	5, 10, and 20 µM	TNBC	NA	Chrysin exerts antimetastatic activities
Lirdpr-apamongkol et al. (44)	2013	Thailand	Breast	10	6 weeks	10–100 µg/ml	4T1cell lines	NA	Chrysin can control metastatic progression and inhibited STAT3 activation
Kasala et al. (45)	2016	India	Lung	6	16 weeks	250 mg/kg b.w	Male Swiss albino mice	NA	Chrysin maintained cellular homeostasis
Brechbuhl et al. (46)	2012	USA	Lung	4 cell lines	NA	5–25 µM	A549; H157; H460; H1975	phase I	Chrysin worked synergistically with doxorubicin to induce cancer cell death
Shao et al. (34)	2012	China	Lung	NA	1 weeks	1 µm	A549	NA	That activation of AMPK by chrysin contributes to Akt suppression, growth inhibition, and apoptosis in human lung cancer cells
Li et al. (47)	2015	China	Colorectal	NA	NA	10–40 µM	HCT-116; HepG2; Hep 3B	G1 phase	That combination of chrysin and cisplatin is a promising strategy for chemotherapy of human cancers
Fu et al. (33)	2007	China	Renal	8	4 weeks	10, 30, and 50 µM	DU145	NA	Chrysin can be a potent inhibitor of angiogenesis and tumorigenesis
Lim et al. (48)	2017	Korea	Lung	6	4 weeks	25 µM	A549	NA	Chrysin extirpates DTX-induced edema as an adverse effect

Table 1 (continued)

Author	Year	Region	Type of cancer	Sample	Duration of study	Dosage of the drug	Animal model/cell line	Phase	Main results
Rehman et al. (49)	2013	India	Renal	6	16 weeks	20 and 40 mg/kg b.w	Male albino Wistar rat	Phase II	Chrysin as an effective chemopreventive agent having the capability to obstruct DEN-initiated and Fe-NTA-promoted renal cancer in the rat model
Khan et al. (50)	2010	India	Hepatic	10	11 Weeks	250 mg/kg b.w	Male albino Wistar rat	NA	Mechanism of action of chrysin occurs through decrease in cell proliferation, induction of cell death by apoptosis and reduction of inflammation
Zheng et al. (51)	,2003	China	Colorectal	NA	1 Weeks	NA	SGC-7901 and HT-29 cells	NA	8-bromo-5-hydroxy-7-methoxychrysin was identified as the most potent anti-HT-29 tumor cells and 5,7-dimethoxy-8-iodochrysin showed the most significant activity against SGC-7901 tumor cells
Maruhashi et al. (52)	2019	Japan	Lung	6	2 Weeks	100 mg	SCC and RERF-LC-AL cell	Plateau phase	Chrysin may be useful as an adjuvant chemotherapy in lung SCC
Lee et al. (53)	2021	Korea	Gastric	NA	NA	25 μM	AGS/FR cell	G2/M phas	Chrysin potentiates the anticancer effect of 5-FU and may be utilized for the treatment of 5-FU-resistant gastric cancer
Bahadori et al. (54)	2016	Iran	Colon	5	6 Weeks	0.5, 1, 2, 4, 8, and 10 mg kg^{-1}	Male BALB/c mice	NA	Chrysin as an efficient apoptosis-based therapeutic agent against colon cancer
Song et al. (55)	2019	Korea	Colon	3	NA	1 mg/ml	HT-29 cell	NA	Chrysin may have efficacy as an anticancer candidate for colon cancer therapy

Table 1 (continued)

Author	Year	Region	Type of cancer	Sample	Duration of study	Dosage of the drug	Animal model/cell line	Phase	Main results
Sun et al. (56)	2012	China	Breast	9	42 days	10, 20, and 40 µM	Xenograft animal model	G0/G1 phase	Orally administered Chrysin potently inhibits tumor growth in mice
Chen et al. (57)	2020	China	Esophageal	5	5 Weeks	10, 25, or 50 mg/kg/day	ESCC cells	NA	Chrysin exerts its anti-cancer effect in ESCC cells via disruption of the assembly of DGKα/FAK complex and resultant blockage of the FAK/AKT signaling pathways
Zhang et al. (58)	2004	China	Cervical	NA	1 Week	NA	Hela cells	NA	Chrysin may be a new potential anti-cancer drug for therapy of human cervical carcinoma

ESCC esophageal squamous cell carcinoma, *SCC* squamous cell carcinoma, *5-FU* 5-fluorouracil, *DTX* docetaxel, *AMPK* AMP-activated protein kinase, *NA* not available

that the inducing properties of apoptosis, anti-proliferative, anti-invasive, anti-metastatic, and anti-angiogenic chrysin increase its anti-cancer potential in vivo (69). Also, chrysin was introduced as an effective apoptosis-inducing agent in colon cancer cells (55). Lirdprapamongkol et al. showed that the hypoxic survival and metastatic growth of breast cancer cells in mice were inhibited by chrysin (44). In another study by Liu H et al., the inhibitory effect of chrysin on the growth of skin cancer was confirmed by inhibition of cyclin-dependent kinases (42).

Shao and colleagues found that chrysin inhibited lung cancer growth and stimulate apoptosis probably via activation of the AMP-activated protein kinase (AMPK) pathway. They observed that chrysin inhibited activation mTOR (Akt/mammalian target of rapamycin), an effect that was reversed by shRNA-mediated knocking down of AMPK. These observations suggest that the activation of AMPK by chrysin can contribute to the inhibition of Akt and apoptosis and induction of cellular proliferation in lung cancer cells. Therefore, the agents involved in AMPK activation can be useful adjuvants along with traditional chemotherapeutics for lung cancer (34) (47). In the rat model, chrysin (20 and 40 mg/kg) shows chemotherapy activity by improving oxidative stress and inflammation in DEN-induced renal carcinogenesis (70). Chrysin suppressed the growth of colon cancer in female Wistar rats by recovering antioxidant mineral levels in the intestinal mucosa, reducing cell proliferation and nitrosative stress (71).

The anti-cancer effects of chrysin have been reported in various models of cancers, including cervical cancer, colorectal carcinoma, leukemia, breast, renal, hepatic, esophagus, skin, thyroid, brain, eye, and prostate cancers. Several studies showed that oral chrysin strongly inhibits tumor growth in mice (33–35, 42, 46). Nevertheless, due to the low bioavailability of flavonoids such as chrysin, there is a need for developing their modified forms, such as synthetic analogues, and designing new drug delivery systems using carriers with different properties.

It is noteworthy that chrysin derivatives have also shown potential antitumor activity, and future studies could also focus on structural modification of chrysin in improving bioavailability and antitumor activity (72, 73). Although chemical modification is a promising strategy in promoting the antitumor activity of chrysin, it seems that nanoscale delivery systems, such as polymer nanoparticles, liposomes, solid lipids, and exosomes, can also promote chrysin cell uptake and increase anti-tumor activity (74).

The present study had some limitations: First, some studies were in the form of dissertations and were excluded due to not being published yet. Second, the full texts of some studies were not available. Third, the lack of a regular framework for reporting results may lead to bias. Finally, some studies were not available due to language limitations.

Conclusion

According to the results of the current systematic review, chrysin inhibits the growth and proliferation of cancer cells by inducing cytotoxic effects. Considering the anti-tumor effects of chrysin, and its safety and non-toxicity towards normal cells, this compound can be considered as an adjuvant along with chemotherapeutic agents in cancer treatment.

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Author Contribution NS and FF1 and FF2 contributed to the design, and MM participated in most of the study steps. SHR and MM and SD and SJ prepared the manuscript. MM and FF1 and FF2 and SHR assisted in designing the study and helped in the, interpretation of the study. All the authors have read and approved the content of the manuscript.

Data Availability Datasets are available through the corresponding author upon reasonable request.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Informed Consent Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

References

1. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–74
2. Stratton M, Campbell P, Futreal P (2009) The cancer genome. Nat [Internet] 458(7239):719–724
3. Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ, Organization WH (2001) Cancer incidence, mortality and survival by site for 14 regions of the world
4. Taheri NS, Nosrat SB, Aarabi M, Tabiei MN, Kashani E, Rajaei S et al (2012) Epidemiological pattern of breast cancer in Iranian women: is there an ethnic disparity? Asian Pac J Cancer Prev 13(9):4517–4520
5. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL (2020) Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 70(6):443–459
6. Rapta P, Mišík V, Staško A, Vrábel I (1995) Redox intermediates of flavonoids and caffeic acid esters from propolis: an EPR spectroscopy and cyclic voltammetry study. Free Radical Biol Med 18(5):901–908
7. Deledda A, Annunziata G, Tenore GC, Palmas V, Manzin A, Velluzzi F (2021) Diet-derived antioxidants and their role in inflammation, obesity and gut microbiota modulation. Antioxidants 10(5):708
8. Azman KF, Zakaria R (2019) Honey as an antioxidant therapy to reduce cognitive ageing. Iran J Basic Med Sci 22(12):1368
9. Jaganathan SK, Mandal M (2009) Antiproliferative effects of honey and of its polyphenols: a review. J Biomed Biotechnol
10. 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(5)
11. Ghosh R, Alajbegovic A, Gomes AV (2015) NSAIDs and cardiovascular diseases: role of reactive oxygen species. Oxid Med Cell Longev 2015:536962
12. Williams CA, Harborne JB, Newman M, Greenham J, Eagles J (1997) Chrysin and other leaf exudate flavonoids in the genus Pelargonium. Phytochemistry 46(8):1349–1353
13. Chen Y-H, Yang Z-S, Wen C-C, Chang Y-S, Wang B-C, Hsiao C-A et al (2012) Evaluation of the structure–activity relationship of flavonoids as antioxidants and toxicants of zebrafish larvae. Food Chem 134(2):717–724
14. Gresa-Arribas N, Serratosa J, Saura J, Solà C (2010) Inhibition of CCAAT/enhancer binding protein δ expression by chrysin in microglial cells results in anti-inflammatory and neuroprotective effects. J Neurochem 115(2):526–536
15. Wang J, Qiu J, Dong J, Li H, Luo M, Dai X et al (2011) Chrysin protects mice from Staphylococcus aureus pneumonia. J Appl Microbiol 111(6):1551–1558
16. Villar IC, Jiménez R, Galisteo M, Garcia-Saura MF, Zarzuelo A, Duarte J (2002) Effects of chronic chrysin treatment in spontaneously hypertensive rats. Planta Med 68(09):847–850
17. Du Q, Gu X, Cai J, Huang M, Su M (2012) Chrysin attenuates allergic airway inflammation by modulating the transcription factors T-bet and GATA-3 in mice. Mol Med Rep 6(1):100–104
18. Duarte J, Jiménez R, Villar IC, Pérez-Vizcaíno F, Jiménez J, Tamargo J (2001) Vasorelaxant effects of the bioflavonoid chrysin in isolated rat aorta. Planta Med 67(06):567–569
19. Torres-Piedra M, Ortiz-Andrade R, Villalobos-Molina R, Singh N, Medina-Franco JL, Webster SP et al (2010) A comparative study of flavonoid analogues on streptozotocin–nicotinamide induced diabetic rats: quercetin as a potential antidiabetic agent acting via 11β-hydroxysteroid dehydrogenase type 1 inhibition. Eur J Med Chem 45(6):2606–2612
20. Critchfield JW, Butera ST, Folks TM (1996) Inhibition of HIV activation in latently infected cells by flavonoid compounds. AIDS Res Hum Retroviruses 12(1):39–46
21. Machala M, Kubínová R, Hořavová P, Suchý V (2001) Chemoprotective potentials of homoisoflavonoids and chalcones of Dracaena cinnabari: modulations of drug-metabolizing enzymes and antioxidant activity. Phytother Res 15(2):114–118
22. Pushpavalli G, Veeramani C, Pugalendi KV (2010) Influence of chrysin on hepatic marker enzymes and lipid profile against D-galactosamine-induced hepatotoxicity rats. Food Chem Toxicol 48(6):1654–1659
23. Anand KV, Mohamed Jaabir MS, Thomas PA, Geraldine P (2012) Protective role of chrysin against oxidative stress in d-galactose-induced aging in an experimental rat model. Geriatr Gerontol Int 12(4):741–750
24. Medina JH, Paladini AC, Wolfman C, de Stein ML, Calvo D, Diaz LE et al (1990) Chrysin (5, 7-di-OH-flavone), a naturally-occurring ligand for benzodiazepine receptors, with anticonvulsant properties. Biochem Pharmacol 40(10):2227–2231
25. Khoo BY, Chua SL, Balaram P (2010) Apoptotic effects of chrysin in human cancer cell lines. Int J Mol Sci 11(5):2188–2199
26. Zeng Y-B, Yang N, Liu W-S, Tang N (2003) Synthesis, characterization and DNA-binding properties of La (III) complex of chrysin. J Inorg Biochem 97(3):258–264
27. Rauf A, Khan R, Raza M, Khan H, Pervez S, De Feo V, Maione F, Mascolo N (2015) Suppression of inflammatory response by chrysin, a flavone isolated from Potentilla evestita Th. Wolf.

In silico predictive study on its mechanistic effect. Fitoterapia 103:129–35
28. Pan M-H, Ho C-T (2008) Chemopreventive effects of natural dietary compounds on cancer development. Chem Soc Rev 37(11):2558–2574
29. Gonzalez CA, Riboli E (2010) Diet and cancer prevention: contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Cancer 46(14):2555–2562
30. Karthikeyan S, Srinivasan R, Wani SA, Manoharan S (2013) Chemopreventive potential of chrysin in 7, 12-dimethylbenz (a) anthracene-induced hamster buccal pouch carcinogenesis. Int J Nutr Pharmacol Neurol Dis 3(1):46
31. Xue C, Chen Y, Hu DN, Iacob C, Lu C, Huang Z (2016) Chrysin induces cell apoptosis in human uveal melanoma cells via intrinsic apoptosis. Oncol Lett 12(6):4813–4820
32. Samarghandian S, Afshari JT, Davoodi S (2011) Chrysin reduces proliferation and induces apoptosis in the human prostate cancer cell line pc-3. Clinics 66:1073–1079
33. Fu B, Xue J, Li Z, Shi X, Jiang B-H, Fang J (2007) Chrysin inhibits expression of hypoxia-inducible factor-1α through reducing hypoxia-inducible factor-1α stability and inhibiting its protein synthesis. Mol Cancer Ther 6(1):220–226
34. Shao JJ, Zhang AP, Qin W, Zheng L, Zhu YF, Chen X (2012) AMP-activated protein kinase (AMPK) activation is involved in chrysin-induced growth inhibition and apoptosis in cultured A549 lung cancer cells. Biochem X Biophys Res Commun 423(3):448–53
35. Yu XM, Phan T, Patel PN, Jaskula-Sztul R, Chen H (2013) Chrysin activates Notch1 signaling and suppresses tumor growth of anaplastic thyroid carcinoma in vitro and in vivo. Cancer 119(4):774–781
36. Rehman MU, Tahir M, Khan AQ, Khan R, Lateef A, Oday OH et al (2013) Chrysin suppresses renal carcinogenesis via amelioration of hyperproliferation, oxidative stress and inflammation: plausible role of NF-κB. Toxicol Lett 216(2–3):146–158
37. Sun LP, Chen AL, Hung HC, Chien YH, Huang JS, Huang CY et al (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(47):11748–11758
38. Zhang T, Chen X, Qu L, Wu J, Cui R, Zhao Y (2004) Chrysin and its phosphate ester inhibit cell proliferation and induce apoptosis in Hela cells. Bioorg Med Chem 12(23):6097–6105
39. Zheng X, Meng WD, Xu YY, Cao JG, Qing FL (2003) Synthesis and anticancer effect of chrysin derivatives. Bioorg Med Chem Lett 13(5):881–884
40. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4(1):1–9
41. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials 11(1):1–8
42. Liu H, Liu K, Huang Z, Park C-M, Thimmegowda N, Jang J-H et al (2013) A chrysin derivative suppresses skin cancer growth by inhibiting cyclin-dependent kinases. J Biol Chem 288(36):25924–25937
43. Yang B, Huang J, Xiang T, Yin X, Luo X, Huang J et al (2014) Chrysin inhibits metastatic potential of human triple-negative breast cancer cells by modulating matrix metalloproteinase-10, epithelial to mesenchymal transition, and PI3K/Akt signaling pathway. J Appl Toxicol 34(1):105–112
44. Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Maruyama T, Athikomkulchai S et al (2013) A flavonoid chrysin suppresses hypoxic survival and metastatic growth of mouse breast cancer cells. Oncol Rep 30(5):2357–2364
45. Kasala ER, Bodduluru LN, Barua CC, Madhana RM, Dahiya V, Budhani MK et al (2016) Chemopreventive effect of chrysin, a dietary flavone against benzo (a) pyrene induced lung carcinogenesis in Swiss albino mice. Pharmacol Rep 68(2):310–318
46. Brechbuhl HM, Kachadourian R, Min E, Chan D, Day BJ (2012) Chrysin enhances doxorubicin-induced cytotoxicity in human lung epithelial cancer cell lines: the role of glutathione. Toxicol Appl Pharmacol 258(1):1–9
47. Li X, Huang J-M, Wang J-N, Xiong X-K, Yang X-F, Zou F (2015) Combination of chrysin and cisplatin promotes the apoptosis of Hep G2 cells by up-regulating p53. Chem Biol Interact 232:12–20
48. Ryu S, Lim W, Bazer FW, Song G (2017) Chrysin induces death of prostate cancer cells by inducing ROS and ER stress. J Cell Physiol 232(12):3786–3797
49. Rehman MU, Tahir M, Ali F, Khan AQ, Khan R, Lateef A et al (2012) Chrysin suppresses renal carcinogenesis via amelioration of hyperproliferation, oxidative stress and inflammation: plausible role of NF-? B. Free Radic Biol Med 53:S50
50. Khan MS, Devaraj H, Devaraj N (2011) Chrysin abrogates early hepatocarcinogenesis and induces apoptosis in N-nitrosodiethylamine-induced preneoplastic nodules in rats. Toxicol Appl Pharmacol 251(1):85–94
51. Zheng X, Meng W-D, Xu Y-Y, Cao J-G, Qing F-L (2003) Synthesis and anticancer effect of chrysin derivatives. Bioorg Med Chem Lett 13(5):881–884
52. Maruhashi R, Eguchi H, Akizuki R, Hamada S, Furuta T, Matsunaga T et al (2019) Chrysin enhances anticancer drug-induced toxicity mediated by the reduction of claudin-1 and 11 expression in a spheroid culture model of lung squamous cell carcinoma cells. Sci Rep 9(1):1–14
53. Lee S, Lee SK, Jung J (2021) Potentiating activities of chrysin in the therapeutic efficacy of 5-fluorouracil in gastric cancer cells. Oncol Lett 21(1):1
54. Bahadori M, Baharara J, Amini E (2016) Anticancer properties of chrysin on colon cancer cells, in vitro and in vivo with modulation of caspase-3,-9, Bax and Sall4. Iran J Biotechnol 14(3):177
55. Song H-Y, Kim H-M, Mushtaq S, Kim WS, Kim YJ, Lim S-T et al (2019) Gamma-irradiated chrysin improves anticancer activity in HT-29 colon cancer cells through mitochondria-related pathway. J Med Food 22(7):713–721
56. Sun L-P, Chen A-L, Hung H-C, Chien Y-H, Huang J-S, Huang C-Y et al (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(47):11748–11758
57. Chen J, Wang Y, Zhao D, Zhang L, Zhang W, Fan J et al (2021) Chrysin serves as a novel inhibitor of DGKα/FAK interaction to suppress the malignancy of esophageal squamous cell carcinoma (ESCC). Acta Pharmaceutica Sinica B 11(1):143–155
58. Zhang T, Chen X, Qu L, Wu J, Cui R, Zhao Y (2004) Chrysin and its phosphate ester inhibit cell proliferation and induce apoptosis in Hela cells. Bioorg Med Chem 12(23):6097–6105
59. Paciello F, Fetoni AR, Mezzogori D, Rolesi R, Di Pino A, Paludetti G et al (2020) The dual role of curcumin and ferulic acid in counteracting chemoresistance and cisplatin-induced ototoxicity. Sci Rep 10(1):1–17
60. San TT, Khaenam P, Prachayasittikul V, Sripa B, Kunkeaw N, Chan-On W (2020) Curcumin enhances chemotherapeutic effects and suppresses ANGPTL4 in anoikis-resistant cholangiocarcinoma cells. Heliyon 6(1):e03255
61. Soni VK, Shukla D, Kumar A, Vishvakarma NK (2020) Curcumin circumvent lactate-induced chemoresistance in hepatic cancer cells through modulation of hydroxycarboxylic acid receptor-1. Int J Biochem Cell Biol 123:105752
62. Lu X, Yang F, Chen D, Zhao Q, Chen D, Ping H et al (2020) Quercetin reverses docetaxel resistance in prostate cancer via

androgen receptor and PI3K/Akt signaling pathways. Int J Biol Sci 16(7):1121
63. Zhang W, Jiang H, Chen Y, Ren F (2019) Resveratrol chemosensitizes adriamycin-resistant breast cancer cells by modulating miR-122-5p. J Cell Biochem 120(9):16283–16292
64. Pichichero E, Cicconi R, Mattei M, Canini A (2011) Chrysin-induced apoptosis is mediated through p38 and Bax activation in B16–F1 and A375 melanoma cells. Int J Oncol 38(2):473–483
65. Weng M-S, Ho Y-S, Lin J-K (2005) Chrysin induces G1 phase cell cycle arrest in C6 glioma cells through inducing p21Waf1/Cip1 expression: involvement of p38 mitogen-activated protein kinase. Biochem Pharmacol 69(12):1815–1827
66. Martins IsL, Charneira C, Gandin V, Ferreira da Silva JL, Justino GaC, Telo JoP et al (2015) Selenium-containing chrysin and quercetin derivatives: attractive scaffolds for cancer therapy. J Med Chem 58(10):4250–65
67. Xuan HZ, Zhang JH, Wang YH, Fu CI, Zhang W (2016) Antitumor activity evaluation of novel chrysin–organotin compound in MCF-7 cells. Bioorg Med Chem Lett 26(2):570–4
68. Khan MS, Halagowder D, Devaraj SN (2011) Methylated chrysin induces co-ordinated attenuation of the canonical Wnt and NF-kB signaling pathway and upregulates apoptotic gene expression in the early hepatocarcinogenesis rat model. Chem Biol Interact 193(1):12–21
69. Kasala ER, Bodduluru LN, Madana RM, Gogoi R, Barua CC (2015) Chemopreventive and therapeutic potential of chrysin in cancer: mechanistic perspectives. Toxicol Lett 233(2):214–225
70. Rehman MU, Tahir M, Khan AQ, Khan R, Lateef A, Qamar W et al (2013) Chrysin suppresses renal carcinogenesis via amelioration of hyperproliferation, oxidative stress and inflammation: plausible role of NF-κB. Toxicol Lett 216(2–3):146–158
71. Sequetto PL, Oliveira TT, Soares ÍA, Maldonado IR, Mello VJ, Pizziolo VR et al (2013) The flavonoid chrysin attenuates colorectal pathological remodeling reducing the number and severity of pre-neoplastic lesions in rats exposed to the carcinogen 1, 2-dimethylhydrazine. Cell Tissue Res 352(2):327–339
72. Zhu Y, Yao X, Long J, Li R, Liu Y, Yang Z, et al (2019) Fluorine-containing chrysin derivatives: synthesis and biological activity. Nat Prod Commun 14(9):1934578X19878921
73. Halevas E, Mavroidi B, Antonoglou O, Hatzidimitriou A, Sagnou M, Pantazaki AA et al (2020) Structurally characterized gallium–chrysin complexes with anticancer potential. Dalton Trans 49(8):2734–2746
74. Moghadam ER, Ang HL, Asnaf SE, Zabolian A, Saleki H, Yavari M et al (2020) Broad-spectrum preclinical antitumor activity of chrysin: current trends and future perspectives. Biomol 10(10):1374