Chrysin targets aberrant molecular signatures and pathways in carcinogenesis (Review)

RITU RAINA[1], RAVINDER BHATT[2] and ARIF HUSSAIN[1]

[1]School of Life Sciences, Manipal Academy of Higher Education-Dubai Campus, P.O. Box 345050, Dubai, United Arab Emirates; [2]Prime Healthcare, Dubai, P.O. Box 7162, United Arab Emirates

Received March 5, 2024; Accepted June 13, 2024

DOI: 10.3892/wasj.2024.260

Abstract. One of the most extensively used herbal medicines is chrysin, a naturally occurring flavone commonly detected in several natural products, including propolis and honey. Due to its various biological properties, such as antioxidant, anti-estrogenic, anti-inflammatory, anti-allergic, antibacterial and anticancer activities, chrysin has emerged as the leading contender for health benefits. Amongst the several pharmacological effects exhibited by chrysin, its anticancer activity is the most attractive. Several studies have demonstrated that chrysin suppresses tumor progression in cell lines and animal models by inducing apoptosis, disrupting the cell cycle and inhibiting migration without generating toxicity or undesired side-effects in normal cells. Furthermore, chrysin also inhibits multi-drug resistant proteins and is effective in combination therapy. The present review comprehensively discusses the research developments in the understanding of the potential of chrysin as a potent anticancer agent achieved by modulating various cell targets and signaling pathways involved in inflammation, cell survival, apoptosis, growth, angiogenesis, invasion and metastasis.

Contents

Correspondence to: Dr Arif Hussain, School of Life Sciences, Manipal Academy of Higher Education-Dubai Campus, P.O. Box 345050, Dubai, United Arab Emirates
E-mail: dr.arifhussain@yahoo.co.in

Key words: chrysin, flavone, anticancer, metastasis, apoptosis, chemotherapeutics, combination

1. Introduction

Compounds with various pharmacological properties can be found in abundance in nature (1). The unique perspective on nature is attributable to the availability of anticarcinogenic medicines with minimal harmfulness and the ability to inhibit a large range of tumors (2). In addition, natural products are less costly and more specific than synthetic medications (3,4). As a result, finding unique phytonutrients, and their therapeutic impact, and releasing them into the market may be regarded as a novel approach to cancer treatment. A number of effective anticancer medicines are either obtained from botanical sources or are molecular modifications of natural compounds (5,6).

Polyphenols found in fruits and vegetables have been shown to attenuate the progression of cancer (4,7-9). Polyphenols such as curcumin, genistein, resveratrol, apigenin, fisetin, luteolin etc., have demonstrated anti-neoplastic activity in a variety of malignancies such as leukemia, breast, cervical, skin, colon etc. by targeting different hallmarks of cancer (10-13). In particular, flavonoids are the most common type of plant secondary metabolites with beneficial health effects, such as antioxidant, anti-inflammatory, anti-allergic and anti-viral properties (8,14). They are ubiquitous polyphenolic phytochemicals, which have been extensively investigated in recent years for their cytotoxic and anticancer properties (6,7). Antioxidant activity, antitumor action, cell cycle halting, the stimulation of self-programmed cell death, the manipulation of signaling pathways, the suppression of cancer cell movement and the increasing efficiency of chemotherapeutics are among the anticancer properties of these agents (11,13,14). Experiments reported recently have revealed the efficacy of flavonoids in cancer treatment. The treatment with natural antitumor substances inhibits the growth of cancer cells with minimal toxicity (1,2,13,15,16). Since these critical molecules

operate through numerous physiological pathways and affect a wide variety of communication networks (6,7), there has been a surge of interest in flavonoids. Flavonoids are predicted to be consumed between 50 and 800 mg per day in the diet (8). The present review discusses the anticancer properties of chrysin, a flavonoid, in various types of cancer as stand-alone candidate and in combination with chemotherapeutics.

Chrysin (5,7-dihydroxyflavone) found in honey and passion flower is a cost-effective and potent anticancer agent. Chrysin possesses numerous biological properties, such as anti-inflammatory, anti-viral, antioxidant and anti-diabetic properties (3,4) (Fig. 1). The most appealing characteristic of chrysin is its anticancer potential, which has been demonstrated through investigations on a wide range of cancer cell lines and animal tumor models. Thus, knowledge of the molecular processes triggered by chrysin in tumor cells may lead to the development of novel cancer treatment approaches with fewer side effects (10). The present review focuses on the anticancer effects of chrysin on various types of cancer and the molecular mechanisms involved.

2. Chrysin structure, sources and pharmacokinetics

Chrysin (5,7-dihydroxy flavone) is a flavone and has a natural 15-carbon structure (Fig. 2). Chrysin is ubiquitously found in passion flower, honey and propolis (3,17,18). Chrysin produced from propolis and honey offers boundless curiosity to researchers (7). Chrysin has two benzene rings (A and B) and one oxygen-containing heterocyclic ring in its structure. It has 2-3 double-bound carbons, with a carbonyl group on the fourth carbon, but no 3-carbon hydroxyl group. Chrysin is classified as a flavone based on its structural categorization. It has -OH groups on the fifth and seventh carbon atoms. Unlike other flavonoids, chrysin has no oxygenation in ring-B. Diverse ring-A oxygenation is primarily responsible for numerous chrysin derivatives, such as wogonin (18,19). The biological actions of chrysin are linked to a lack of oxygenation in the B and C rings, which is associated with anti-inflammatory and antitoxic properties. Flavones show different levels of oxidative potential which is reliant on their difference in structure. The antioxidant property of chrysin is dependent on carbonyl group on C4 and double bond between C2 and C3. At lower doses, flavones are beneficial; however, they can be toxic at higher doses and the recommended dose for chrysin is <3 g/day (18,20).

Chrysin has an extremely low bioavailability in humans due to rapid quick metabolism, removal and restricted assimilation. The bioavailability of chrysin when taken orally has been estimated to be between 0.003 to 0.02% (21). In intestinal and hepatic cells, chrysin undergoes metabolism primarily by conjugation processes (glucuronidation and sulfation) and less by oxidation (22). The highest concentrations of chrysin sulfate and glucuronide have been found in the bile in studies on chrysin metabolism in mice (23). As a result, excretion through feces is the main recommended method for the elimination of chrysin and its metabolites (22,23). Chrysin sulfonate and glucuronide have been found in the urine and plasma at low concentrations (22). The poor bioavailability of chrysin has been best addressed by encapsulating it in nanoparticles (24). One of the optimal methods with which to obtain a therapeutic drug delivery platform to treat recurrent oral ulcers and increase chrysin bioavailability is to entrap the drug in niosomal oromuco-adhesive films (25). The release kinetics and cytotoxicity of chrysin are also regulated by encasing it in poly (d, l-lactic-coglycolic acid) poly (ethylene glycol) (PLGA-PEG) nanoparticles (26). Notably, chrysin has been proven to be safe and effective in various studies where volunteers have taken oral doses ranging from 300 to 625 mg without experiencing any documented effect (10,27).

3. Chrysin and its pharmacological activities

Chrysin has been observed to be beneficial in various metabolic disorders, such as diabetes, cardiac disease, neurodegenerative diseases and above all, cancer (28). In both human and animal cancer models, it has been shown that tumors release cytokines, immunological mediators, classical neurotransmitters, pituitary and hypothalamus hormones, melatonin and glucocorticoids. The body and brain activities can be impacted by catecholamines, serotonin, melatonin, neuropeptides and other neurotransmitters generated from tumors. Cancers can take over the immunological and neuroendocrine systems, resetting the body's equilibrium to favor their growth at the expense of the host (29). Chrysin has been shown to exert neuroprotective effects via a variety of mechanisms, such as gamma-aminobutyric acid mimetic properties, monoamine oxidase inhibition, antioxidant, anti-inflammatory and anti-apoptotic activities (30).

Elevated glucose levels have been shown to cause self-programmed death in glomerular specialized cells, and this process can be minimized following treatment with chrysin (18). The main mechanism involved in the effects of chrysin is the decrease in the splitting of DNA and the repair of ratio of Bax and Bcl-2, as well as the inhibition of cytochrome *c* and apoptotic protease activating factor 1 in glomerular cells subjected to a higher concentration of glucose (18,31). Chrysin therapy has been shown to reduce NF-κB p65 unit, TNF-α, IL-1, IL-6 and caspase-3 levels in the cerebral cortex and hippocampus, resulting in the antidiabetic protection of cognitive decline (32). The use of chrysin also results in reduced blood sugar and insulin signaling molecules and glucose tolerance inhibition (33). Another study revealed that treatment with chrysin between 20-80 mg/kg/day decreased the levels of low-density lipoprotein cholesterol, triglycerides and cholesterol, and at the same time increased the levels of high-density lipoprotein cholesterol, glutathione S-transferase, superoxide dismutase and catalase (34). Chrysin is a potent antioxidant and this has been reported by various studies. In rats, chrysin has been shown to reduce lipid peroxidation, increase antioxidant enzyme levels, decrease the expression of p53 and intrinsic apoptosis-related proteins, including Bax, Noxa, cytochrome *c* and caspase-3, increase the activity of Bcl-2, inactivate the MAPK/JNK pathway and suppress the NF-κB pathways, and at the same time upregulate the expression of PTEN, and activate the VEGF/AKT pathway (Fig. 3) (18,35). Chrysin inhibits cytochrome P450 2E1, alcohol dehydrogenase and xanthine oxidase at various dosages (20 and 40 mg/kg body weight) and protects Wistar rats against oxidative stress. It also reduces serum aspartate aminotransferase, alanine aminotransferase and glutamate aminotransferase levels (36).

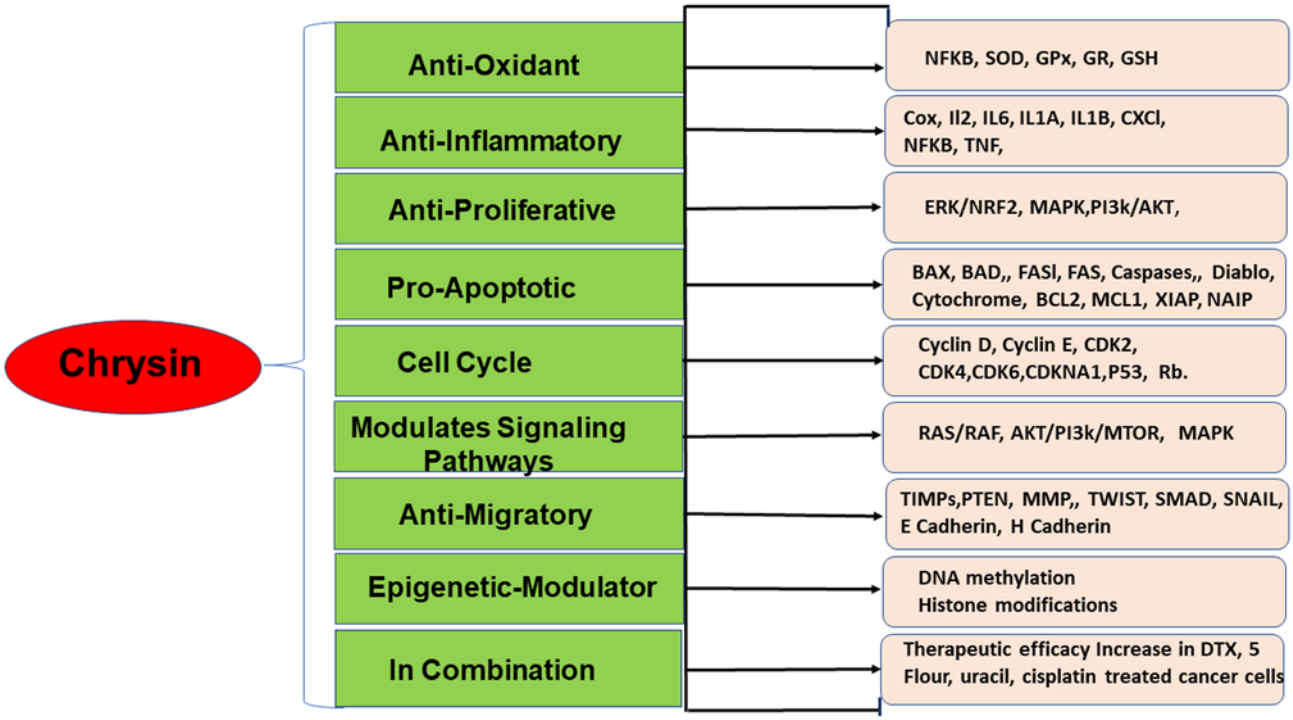

Figure 1. Schematic illustration of the different pharmacological properties of chrysin and the involvement of different molecules in these pathways. Chrysin acts as a potent anticancer agent, inducing apoptosis, inhibiting cell proliferation and migration, and all the proteins related to these molecular pathways. SOD, superoxide disumate; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; TIMP, tissue inhibitor of metalloproteinases; MMP, matrix metalloproteinase.

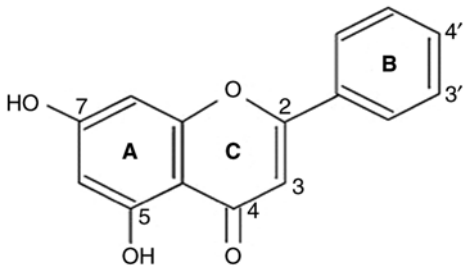

Figure 2. Chemical structure of chrysin.

4. Literature search methodology used

To identify published research, searches were conducted using databases, such as Medline, PubMed, Scopus, Science Direct and Google Scholar. Of note, two authors conducted a literature search for this purpose using the terms chrysin, anticancer, cancer therapy, chemotherapeutics and their combinations. In addition, an investigation of the references of the article was performed to search for any further research. The search approach was used to filter the article titles and abstracts.

5. Mechanistic details of the anticancer potential of chrysin

Chrysin demonstrates anticarcinogenic action in a number of leukemias and most solid cancers. Chrysin has been shown to have beneficial effects against numerous types of cancer, including hepatic, breast, lung, cervical and prostate carcinomas (10,37) (Fig. 3). Chrysin reduces cancer growth by selectively modulating various cell signaling pathways associated with inflammation, cancer cell survival, proliferation, angiogenesis, invasion and metastasis. A number of studies have reported the anticancer properties of chrysin in cell lines, as well as animal models, demonstrating different pathways (10,37-39) (Fig. 3). A previous study demonstrated that the chrysin treatment in ovarian cancer led to the augmented generation of reactive oxygen species, a decrease in MMP and an increase in cytoplasmic Ca^{2+}, together with the initiation of cell demise (40). Chrysin has been shown to promote the apoptosis of lymphocytic leukemia cells, via the mitochondrial pathway (41). It has been found that chrysin has no cytotoxic effect on normal cells, such as fibroblasts (42). Additionally, chrysin has depicted notable anticancer effects in combination with chemotherapeutic drugs by overcoming resistance (43) (Fig. 4). The present review discusses the anticancer effects of chrysin in various types of cancer alone and in combination (Figs. 1, and 3-5) with chemotherapeutic agents.

6. Chrysin in cervical cancer

The term 'cervical cancer' refers to a malignant tumor that arises from cells in the cervix uteri (44,45). It is a malignancy which frequently affects women and is considered to be one of the chief reasons of cancer-related mortality worldwide (46-48). According to the WHO 2021 report, it is the fourth most frequent type of cancer among women globally, both in regards of prevalence and mortality rates, with an estimated 6 lakhs new cancer cases and 3.5 lakh deaths (49). The primary cause of cervical cancer is manifestation of human papillomavirus (HPV), and virtually all cervical cancers include

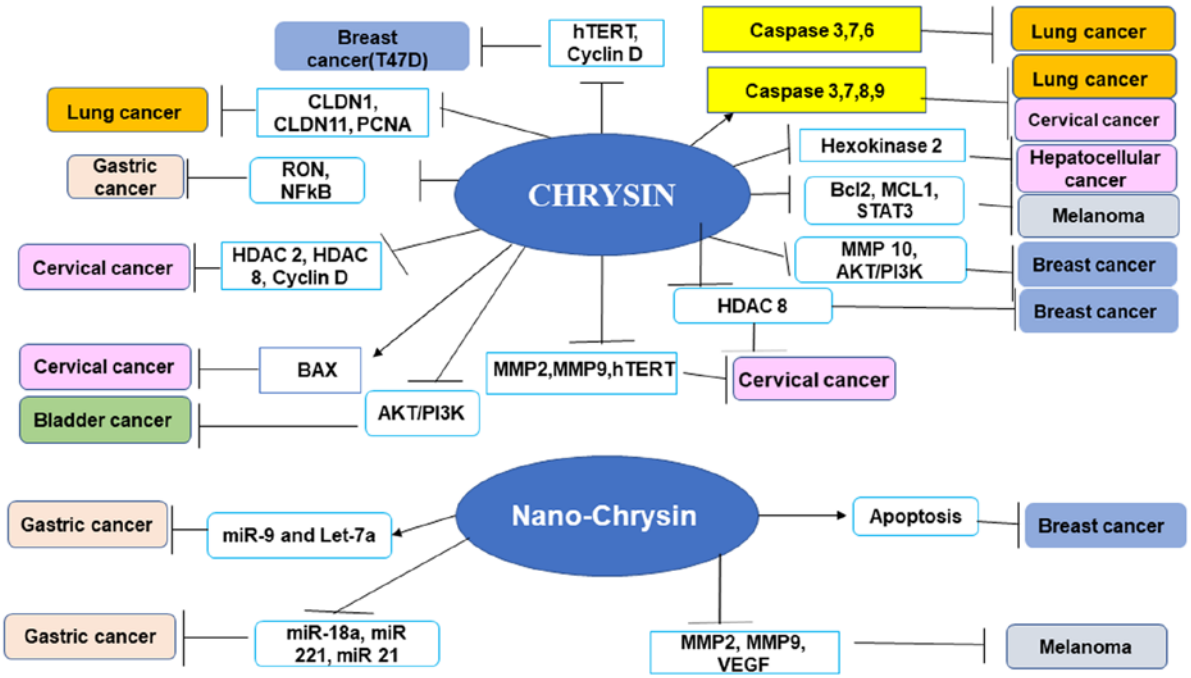

Figure 3. Schematic illustration of the effects of chrysin on different molecular and cellular pathways in different types of cancer. In breast cancer, chrysin inhibits MMP10, AKT/PI3K, hTERT, cyclin D and nano-chrysin induces apoptosis and inhibits migration. In cervical cancer, chrysin impedes anti-apoptotic proteins, MMPs and augments pro-apoptotic proteins, causing cell death. In lung cancer, chrysin hinders CLDN1, CLDN11 and PCNA, and activates all caspases, leading to anti-proliferative effects. In bladder cancer, chrysin suppresses RON and NF-κB. In gastric cancer, chrysin impedes RON, NF-κB and nano-chrysin inhibits miR-9 and Let-7a and miR-18a, miR-221, miR-21 leading to inhibition of proliferation. In melanoma cells, chrysin constrains Bcl-2, MCL1, STAT3 and nano-chrysin impedes MMP2, MMP9, VEGF causing apoptosis. RON, recepteur d'origine nantais; MMP, matrix metalloproteinase; MCL1, myeloid cell leukemia-1.

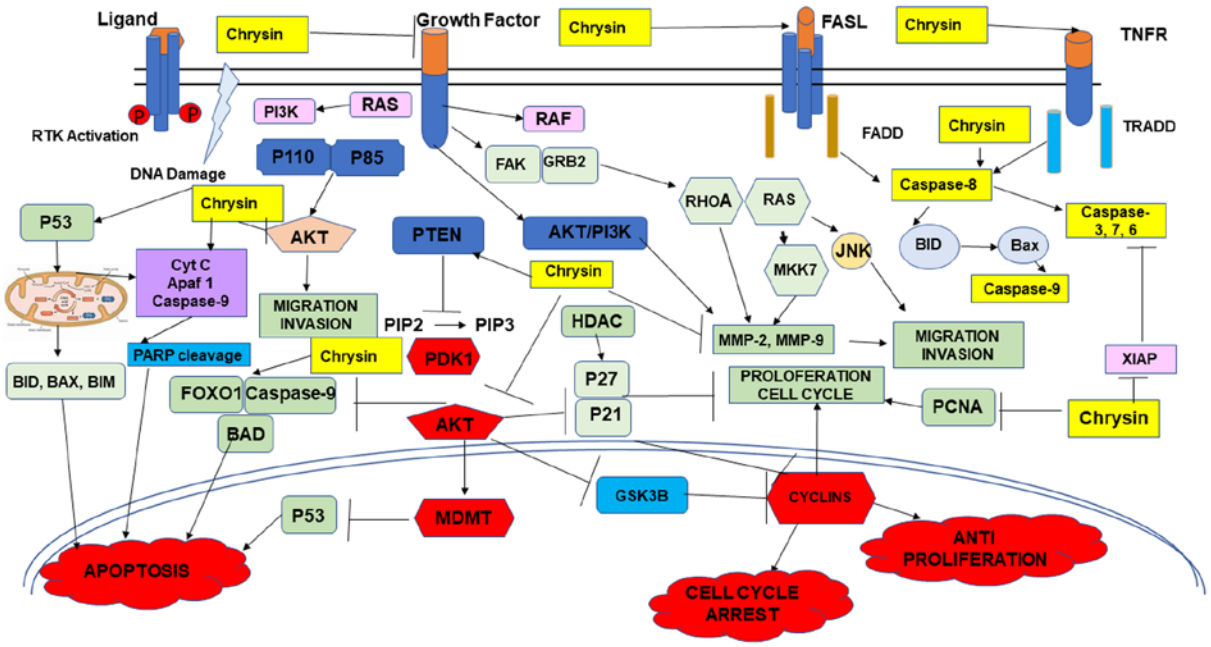

Figure 4. Schematic illustration of the role of chrysin in targeting different hallmarks of cancer, namely apoptosis, proliferation, migration and cell cycle arrest by the modulation of different genes. Chrysin activates all pro-apoptotic apoptotic proteins, such as Bax, caspases, CytC and Apaf1, and inhibits anti-apoptotic and migratory proteins. Chrysin inhibits AKT/PI3K pathways, thus hindering cell growth and preventing migration. Chrysin activates PTEN, which impedes the AKT pathway. PTEN, phosphatase and tensin homolog; HDAC, histone deacetylase; GRB2, growth factor receptor-bound protein 2; PCNA, proliferating cell nuclear antigen.

one or more HPV genotypes (50,51). There are no antiviral therapies available for HPV infection; however, prophylactic vaccination is an excellent primary preventive technique for cervical cancer (52,53). Gardasil 9 has been approved for nine types of HPV types (16 and 18 being most prevalent) and also, these vaccinations provide minimal benefit to those who are

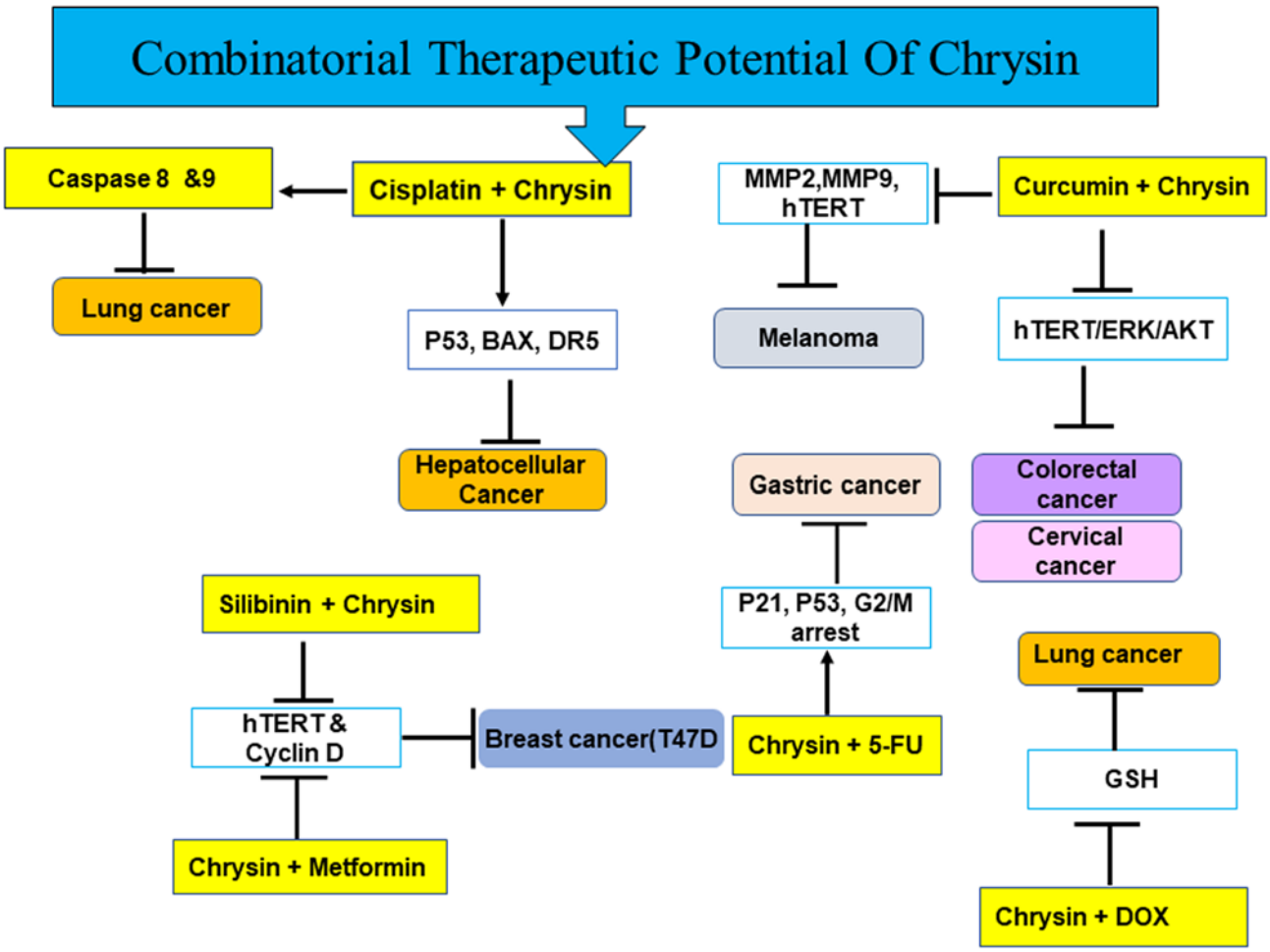

Figure 5. Schematic illustration of the anticancer effects of chrysin in combination with chemotherapeutic drugs and chemo-preventive agents, such as cisplatin, 5-fluorouracil, doxorubicin, metformin and curcumin. The combination of chrysin with curcumin re-sensitizes cancers, such as cervical, colorectal and melanoma cancers to chemotherapeutic drugs. Chrysin in combination with cisplatin leads to increased apoptosis in hepatocellular carcinoma. Chrysin in combination with silibinin and metformin inhibits breast cancer cells. hTERT, human telomerase reverse transcriptase; MMP, matrix metalloproteinase.

previously infested with the virus, and also are unavailable to general populations in developing countries where cervical cancer is prevalent maximum (52-54). There are various chemotherapeutics available for cervical cancer treatment; however, they all have severe side-effects; hence, the search for selective cancer treatment strategies with which to reduce the cervical cancer morbidity and motility continues (3,11).

Various studies have reported the anticancer effects of chrysin on different types of cervical cancer cells (Table I). Chrysin incudes the death of cervical cancer cells via the modulation of various pathways, such as MAPK, AKT/mTOR and genes responsible for tumor growth (Fig. 3) (4). Chrysin also induces apoptosis via PI3K pathway in HeLa cells (55) Chrysin likewise downregulates proliferating cell nuclear antigen (PCNA) expression in cervical carcinoma cells (10). Chrysin at a dose of 30 μM has also been shown to promote nuclear factor kappa-light-chain-enhancer of activated B-cells in HeLa cells (56,57). Additionally chrysin reactivates various TSGs and genes related to apoptosis and migration by decreasing the methylation percentage of these genes, and decreasing the expression of various epigenetic enzymes, such as DNA methyl transferase, histone acetyl transferase, histone deacetyl transferase and histone methyl transferase at the biochemical and transcript level, leading to the modulation of H3 and H4 histone modification marks and decreased DNA methylation following the treatment of Hela cells with chrysin (37). Chrysin encourages TRAIL-induced apoptosis by sensitizing HeLa cells to chrysin (58). Chrysin functions as a dual inhibitor of methylation at the DNA and histone level (59). Chrysin decreases the expression of TWIST 1 and NF-κB and thus suppresses epithelial-mesenchymal transition (EMT) in HeLa cells (60).

In addition to the anticancer effects of chrysin used alone, the use of chrysin in combination with other chemotherapeutics and natural compounds has depicted additional effects. It has been shown that chrysin and capsaicin promote early senescence and programmed cell death via mitochondrial dysfunction and an increase in p53 levels (61). Chrysin and cisplatin have also been shown to exert synergistic effects on induction of apoptosis and the inhibition of migration (62) (Table II).

7. Chrysin in breast cancer

Breast cancer is the most prevalent and lethal type of cancer affecting women (63). The efficacy of commonly used

Table I. The concentrations/doses of chrysin in the treatment in cervical and breast cancer cells/animal models.

Authors, year of publication	Cancer type	Cell line/animal model	Concentration/dose	Mechanism of action	(Refs.)
Dong *et al*, 2019	Cervical cancer	HeLa Cells	10, 20, 40 μM	Inhibition of EMT, NF-κB and suppressing migration.	(60)
Raina *et al*, 2019	Cervical cancer	HeLa Cells	15, 20, 25 μM	Induction of apoptosis via downregulation of AKT/mTOR/PI3K.	(4)
Lirdprapamongkol *et al*, 2013	Cervical cancer	HeLa cells	20, 40 60 μM	Inactivation of STAT/MCL1 for sensitization of TRAIL-resistant cervical cancer cells	(58)
Raina *et al*, 2022	Cervical	HeLa	5,10 and 15 μM	Downregulation of MMPs, SMAD, SNAIL and upregulation of TIMP, E-cadherin and SOCS1.	(37)
Raina *et al*, 2022	Cervical cancer	HeLa	5, 10 and 15 μM	Decrease of promoter methylation and reactivation of TSGs. Decreased H3K27, K9, K36, K79, K4 methylation and H4K5, H4K8, H4K12, H4k16.	(37)
Kanwal *et al*, 2016	Cervical cancer	HeLa	10 and 20 μM	Chrysin acts as a dual inhibitor of DNA methylation and histone methylation.	(59)
Sun *et al*, 2012	Breast cancer	MDA-MB-231 cells/ xenograft animal model	40 μM/45/90 mg/kg B.W/day for 6 weeks	Chrysin acts as a HDAC 8 inhibitor and inhibits tumor growth.	(71)
Lirdprapamongkol *et al*, 2013	Breast cancer	4T1/Balb/c mice implanted with 4T1 cells	60-100 μM/100 & 250 mg/kg B.W for 31 days	Oral administration of chrysin inhibits metastasis/ STAT3	(58)
Samarghandian *et al*, 2016	Breast cancer	MCF-7	IC50 of 19.5 and 9.2 M for 48 and 72 h	Chrysin induced apoptosis in MCF cells.	(70)
Anari *et al*, 2016	Breast cancer	T47D & MCF7	5-640 μM of pure and nano-encapsulated chrysin	PLGA-PEG loaded chrysin enhanced the cytotoxicity toward the breast cancer cell lines.	(79)
Yang *et al*, 2014	Human triple-negative breast cancer	TNBC cell line	Chrysin 5, 10 and 20 μM	Modulating matrix metalloproteinase-10, epithelial to mesenchymal transition, PI3K/AKT signaling pathway.	(68)

Table II. The concentrations/doses of chrysin and chemotherapeutic drug combinations in different cancer cells/animal models and their effects.

Authors, year of publication	Cancer type	*In vitro/in vivo*	Combination	Mechanism of action	(Refs.)
Raina *et al*, 2023	Cervical cancer	HeLa cells	Chrysin 4 μM and cisplatin 1.5 μM	The synergistic anti-cancer effect observed. Augmented apoptosis and prevented migration.	(62)
Pawar *et al*, 2022	Cervical cancer	HeLa cells	Chrysin and capsaicin	Induction of ROS, leading to initiation of apoptosis and senescence.	(61)
Lee *et al*, 2021	Gastric cancer	AGS/FR	25 μM 5-fluorouracil/50 μM chrysin	Chrysin and 5-FU showed synergistic anticancer effects and overcame 5-FU resistance *in vitro*.	(43)
Lim *et al*, 2017	Lung cancer	A549-derived xenograft model/BALB/c nude mice	10 to 0.625 ng/ml DTX and 100 to 10 μM chrysin; 25-50 mg/kg B.W chrysin/25-50 mg/kg B.W docetaxel	*In vivo/vitro*, chrysin enhanced the tumor growth delay of DTX and increasedDTX-induced apoptosis in the A549-derived xenograft model.	(89)
Shao *et al*, 2012	Lung cancer	A549	1 μM DOX/1 μM Chr	Chrysin facilitated doxorubicin-induced AMPK activation and instigated apoptosis in A549 cells.	(81)
Brechbuhl *et al*, 2012	Lung cancer	H157 H1975 and H460	5-30 μM chrysin and DOX (0.025-3.0 μM)	Chrysin worked synergistically with DOX to induce cancer cell death.	(91)
Tavakoli *et al*, 2018	Melanoma cancer cells	B16F10/Healthy male C57B16 mice and B16F10 melanoma tumor model	Cur 5 to140 μM, Chr 20 to 180 μM. Encur, chr 5 to 60 μM Cur (15 mg/kg), nano-encapsulated Cur (30 mg/kg), pure Chr (15 mg/kg) and nano-encapsulated Chr (30 mg/kg) in groups.	Combination augmented the decrease in telomerase, MMPs and TIMPs gene expression.	(105)
Gao *et al*, 2018	Hepatocellular cancer	BEL-7402/ADM	10 and 20 μM chrysin/8 μM doxorubicin	Chrysin enhances sensitivity of BEL-7402/ADM cells to doxorubicin.	(119)
Li *et al*, 2015	Hepatocellular cancer	Hep G2 cancer cells.	40 μM chrysin/cisplatin (5 mg/ml)	Combination of chrysin and cisplatin increased the phosphorylation and accumulation of p53 through activation of ERK1/2 and pro-apoptotic protein.	(120)
Lotfi-Attari *al*, 2017	Colorectal cancer	Human epithelial colorectal/adenocarcinoma cell line (Caco-2)	10-45 μM chrysin (chr)/ curcumin(cur) 5-15 Free and encapsulated	Chr/Cur nano synergistically therapy has showed downregulation of hTERT and MMPs.	138)
Szliszka *et al*, 2010	Bladder cancer	RT112	20-80 μM	Chrysin enhances the effect of TRAIL in bladder cancer cells.	
Rasouli *et al*, 2018	Breast Cancer	Breast cancer cells T47D	Chrysin 62.70 μm, 24 h; 44.78 μm, 48 h; metformin, 18.08 mM, 24 h 15.54 mM-48 h	Combination of chrysin and metformin synergistically inhibited cell growth by inhibition of hTERT and cyclin D	(69)

Table II. Continued.

Authors, year of publication	Cancer type	*In vitro/in vivo*	Combination	Mechanism of action	(Refs.)
Javan *et al*, 2019	Breast Cancer	MDA-MB-231	Free curcumin, chrysin-14.14, 28.28 Curcumin and chrysin-NPs 9.988, 19.9 μM	Curcumin and Chrysin showed a significant cooperative cytotoxicity, cell cycle arrest at G2/M phase and apoptosis through upregulation of expression of miR-321 and miR-502c in comparison to alone drugs.	(80)
Zhang *et al*, 2021	Colorectal cancer	HCT 116 and SW480	25 μM chrysin + 25 μM of apigenin	Apigenin and chrysin together encouragingly repressed the development and migration of CRC cells by reducing P38-MAPK/AKT activity.	(137

5-FU, 5-fluorouracil; Cur, curcumin; DOX, doxorubicin; Chr, chrysin; DTX, docetaxel.

treatments in breast cancer therapy has been limited by recurrence and chemoresistance (64,65). Natural products, including flavonoids have been shown to exert a potent inhibitory effect on breast cancer growth and metastasis (11,66,67). These natural compounds possess anticancer and anti-cell migration properties, and enhance the efficiency of chemotherapeutic drugs (11). It has been shown that chrysin alone modulates the PI3K/AKT pathway (Table I) and when used in combination (Table II), it exerts anticancer effects on breast cancer cells by modulating human telomerase reverse transcriptase (hTERT) and cyclin D in breast cancer cells (11,68,69).

Previous research has demonstrated that chrysin suppresses the proliferation in the MCF-7 breast cancer model in a dose and time-dependent manner with IC50 values of 19.5 and 9.2 M for 48 and 72 h, respectively (34,70). This anti-proliferative action is credited to its capability to induce the apoptosis of these cancer cell lines. Chrysin significantly inhibits histone deacetylase (HDAC)8 activity with an IC50 of 40.2 μM that significantly decreased the progression of breast cancer (MDA-MB-231). It was previously shown that the oral administration of 90 mg/kg/day of chrysin for 6 weeks evidently decreased tumor size in the MDA-MB-231 xenograft model. Chrysin administration led to the upregulation of CDKN1 at the transcript and protein level (71). Chrysin decreased the viability of 4T1 breast cancer cells by suppressing hypoxia-induced phosphorylation of STAT3 and suppressed hypoxia-induced VEGF gene expression. A similar effect was observed in animal models implanted with 4T1 cells (42,72). Chrysin also obstructs the migratory capacity of metastatic human triple-negative breast cancer cells by modifying MMP10, EMT transition, and PI3K/AKT pathway (68) (Table I). Another study demonstrated that chrysin-loaded PGLA/PEG nanoparticles modulated TIMPS and MMP2 and 9, and PI3K expression in a mouse 4T1 breast tumor model (73).

In addition to its stand-alone anticancer properties, chrysin has been shown to enhance the efficiency of chemotherapeutic drugs. Nano technology has further increased the efficiency of drugs (74). Chrysin and metformin in combination have been found to exert anti-proliferative effects against T47D breast cancer cells. Chrysin used alone and as an adjuvant with metformin has been found to downregulate cyclin D and hTERT expression in the breast cancer cell line (69). Similar results were obtained with the combination of chrysin and silibinin in T47D breast cancer (75). Another study demonstrated that chrysin ruthenium complex promoted the apoptosis of MCF-7 cancer cells via the modulation of Bcl-2, p53 and Bax (76). It has been shown that nano-chrysin inhibits the proliferation of SKOV-3 and MCF-7 cells in a concentration-dependent manner. Nano-chrysin had a much lower IC50 value than pure chrysin and triggers the apoptosis of cancer cells (77). Polymeric micelles have also been created to administer chrysin and methotrexate to breast cancer cells during chemotherapy (78). It has been found that PLGA-PEG loaded with chrysin increases the solubility of the drug and decreases the disputatious effects of chrysin. Chrysin proficiently collects in the T47D cancer cells and augments the cytotoxicity of chrysin on breast cancer cells (79). The combination of chrysin and silibinin decreases the expression hTERT and cyclin D1 in T47D breast cancer cells (75) (Fig. 5).

Curcumin and chrysin have been shown to exert significant cooperative cytotoxicity, halt the cell cycle at the G2/M stage and promote apoptosis through the upregulation of expression of miR-321 and miR-502c in comparison to the drugs used alone (80) (Table II).

8. Chrysin in lung cancer

Lung cancer is one of the principal causes of cancer-related mortality (81,82). In spite of the major advances being made in diagnosis and therapy, the overall 5-year survival rate of patients with lung cancer remains <20% (83). Resistance to chemotherapy and radiation has been identified as the key impediments to effective treatment, and novel adjuvants are urgently required. As a result, it is critical to investigate new targeted agents for lung cancer (81). Flavonoids are phenolic chemicals found in plants that have antibacterial, antiviral, anti-inflammatory, anti-allergic, anti-thrombotic, anti-mutagenic and anti-neoplastic effects (84).

Chrysin (5,7-dihydroxyflavone) is a naturally occurring flavonoid found in several therapeutic plants (4,28). The anti-proliferative abilities of chrysin against human lung cancer cells have been established by a number of research groups (28,81) (Table III). Treatment with chrysin has been shown to lead to the activation of AMPKA and the suppression of AKT, the induction of apoptosis and the growth inhibition of A549 lung cancer cells (81).

CLDN1 and CLDN11 expression have been found to be higher in human lung squamous cell carcinoma. Treatment with chrysin treatment reduces both the mRNA and protein expression of these claudin genes (85) (Fig. 3). Chrysin exerts cytotoxic effects on and promotes the death of human lung cancer and lymphoma cells from mice at doses ranging from 25 to 75 g/ml, with no overt damage to normal cells. Chrysin induces G1/S phase arrest at specific doses. Treatment with chrysin treatment (1.3 mg/kg body weight) significantly decreases tumor volume, resulting in a 52.6% increase in mouse survival (86).

Chrysin restores the cellular equilibrium of cells subjected to benzopyrene by downregulating the expression of elevated proteins, such as PCNA, NF-κB and COX-2 (7,42). Chrysin promotes the apoptosis of lung adenocarcinoma cells via the modulation of caspases, Bax and Bcl-2 (87). Chrysin, together with doxorubicin, promote the activation of AMPK to induce A549 programmed cell death which is attributed to AKT inhibition (81). It has also been shown that chrysin can prevent the constitutive activation of STAT3, leading to the decreased expression of myeloid cell leukemia-1 (Mcl-1); this action motivates the deactivating TRAIL resistance of A549 human lung cancer cells by chrysin (58). A previous study demonstrated that quercetin and chrysin together decreased the levels of pro-inflammatory molecules, such as IL-6, -1 and -10, and the levels of TNF via the NF-κB pathway. In addition, chrysin and quercetin downregulated the expression of Myd88 and Toll-like receptor 4, as well as MMP9 (88). Chrysin has been shown to increase the efficacy of docetaxel in non-small cell lung cancer by inducing cytotoxicity, suppressing cell proliferation and promoting apoptosis (89) (Fig. 5). A previous study demonstrated that in A549 lung cancer cells, curcumin- and chrysin-loaded nanoparticles led to the downregulation of hTERT and MMPs (90). Another study demonstrated that the combination of chrysin and doxorubicin decreased the IC50 value of four cell lines, namely H460, A549, H157 and H1975 (91). Chrysin at concentrations between 5 and 30 μM and doxorubicin at concentrations between 0.025 and 3.0 μM in combination functioned synergistically in lung cancer cells to induce cell death and reduce the toxicity of doxorubicin (91) (Table II). However, despite the numerous biological properties of chrysin, its limited bioavailability is the primary barrier to its use in pharmaceuticals. Chrysin-loaded nanoparticles have depicted improved therapeutic activity in animal models and may serve as a useful formulation for pharmacological intervention (89).

9. Chrysin in melanoma and non-melanoma cells

Skin cancer is a common disease that affects numerous individuals worldwide. The increase in the number of skin cancer cases over the past few decades may be due to multiple factors. These could include individual and collective habits, as well as changes in the climate, particularly in the ozone layer. The most common types of skin cancer encountered by physicians are melanomas and non-melanomas. More specifically, there are two forms of non-melanoma cancer: Squamous cell carcinoma and basal cell carcinoma (92). The prognosis of patients with this type of cancer is typically very poor (93). Of note, 80% of skin malignancies that are not melanomas are caused by basal cell carcinoma. UV radiation exposure is the main factor that may result in basal cell carcinoma. Aggressive melanomas account for 60% of skin cancer-related mortality, despite representing only 1% of all cases of skin cancer cases (94). Chrysin has been shown to inhibit squamous cell carcinoma via the modulation of Rb and by decreasing the expression of CDK2 and CDK4 (95).

Melanoma is an extremely resistant and aggressive skin tumor that accounts for >2-3% of all cancer occurrences. Melanoma incidence has risen dramatically in recent decades and is responsible for more than 75% of all skin cancer fatalities due to its aggressiveness (96,97). Melanoma can be treated with surgery in its early stages; however, treatment is impossible after it metastasizes to other areas (97). As melanin synthesis occurs inside the specialized membrane-bound organelles known as melanosomes, it is a highly regulated process in normal melanocytes. Under these circumstances, the synthesis of melanin serves as a defense against attacks from the environment and UVR-induced malignancies. However, melanin pigment appears to have a function in the malignant transformation of melanocytes despite its protective effect against UVR (98). This process can become dysregulated in melanoma cells when melanogenesis intermediates seep outside of melanosomes, influencing the behavior of the cells or the environment around them (99). Thus, unchecked melanogenesis plays a role, perhaps a crucial one, in the development of melanotic melanoma and, in conjunction with melanin pigment, it can reduce the effects of chemo- and radiotherapy. The protective properties of melanin pigment under normal circumstances and its destructive properties under pathological ones represent the yin and yang of melanogenesis (98).

Table III. The concentrations/doses of chrysin in lung and melanoma cell lines/animal models.

Authors, year of publication	Cancer type	Cell line/animal model	Concentration/dose	Mechanism of action	(Refs.)
Samarghandian *et al*, 2014	Lung cancer	A549	0 to 15 μM chrysin	Chrysin induces the apoptosis of lung cancer cells. chrysin impedes the development of the lung cancer cells by encouraging cancer cell programmed cell death.	(87)
Kasala *et al*, 2016	Lung cancer	Male Swiss Albino mice	250 mg/kg B.W chrysin	Chrysin downregulated PCNA, COX-2 and NF-κB	(7)
Shao *et al*, 2012	Lung cancer	A549	1-10 μM chrysin	Chrysin treatment led to activation of AMPKA and suppression of AKT, induction of apoptosis.	(81)
Maruhashi *et al*, 2019	Lung cancer	SCC and RERF-LC-All cell	100 mg chrysin	Chrysin decreased CLDN1 and CLDN11 expression in lung cancer. RERF-LC-AI cells and increased the cytotoxicity of Dox.	(85)
Xue *et al*, 2016	Melanoma cells	SP6.5 and M17 cell line	0, 10, 30 and 100 μM	Chrysin induced apoptosis in melanoma cells via mitochondrial pathway and had no effect on scleral fibroblasts and retinal pigment epithelial (RPE) cells.	(101
Chen *et al*, 2019	Melanoma cells	A375.S2 cells	10-15 μM chrysin	Chrysin inhibits migration by downregulation of MMPs and NF-κB and MAPK pathways	(103)
Yufei *et al*, 2020	Melanoma cells	A375 cells/C57BL/ 6 mouse model of lung metastasis	5, 10 and 15 μM chrysin/100 mg/Kg B.W	Chrysin impedes melanoma tumor metastasis via distressing with the FOXM1/β-Catenin signaling pathway.	(104)
Sassi *et al*, 2018	Melanoma cells	B16F10 cells/ Balb C mice were injected with	12.5, 25, 50 &100 μM chrysin/(50 mg chrysin/kg of B.W.) 14/21 days	Chrysin inhibited cell growth, arrested the cell cycle at the G2/M phase and induced apoptosis on melanoma. Cells *in vitro*. Moreover, chrysin augments the function of natural killer cells, cytotoxic lymphocytes, and macrophages, in B16F10-induced melanoma BALB/c mice.	(96)

Bioactive compounds, including chrysin derived from plants, are able to induce apoptosis, as well as hinder migration; they have been evaluated as possible medications in melanoma treatment (100,101). *In vitro*, it has been shown that chrysin selectively exhibits toxicity and induces the self-programed death of human uveal melanoma cells (M17 and SP6.5) without having any effect on normal cells (101). *In vitro* and *in vivo*, chrysin has been shown to exert profound toxicity against melanoma cells (Table III) by encouraging self-programed death along with halting the cell cycle at the G2/M or G1/S phases. In animal models, 2 and 3 weeks of treatment with chrysin was found to decrease the tumor volume by >55 and >65%, respectively (96,101) O note, chrysin promotes the toxicity of natural killer cells, T-cells and macrophages, towards cancer cells) (96). MMPs, such as MMP2 and MMP9 play a prominent role in cancer cell migration via the degradation of the extracellular matrix (102). Chrysin inhibits the migration of melanoma cells and HeLa cells via the downregulation of MMP2, and the upregulation of E-cadherin and the downregulation of cadherin (37,103). The AKT/PI3K and NF-κB pathways play a role in cancer cells and chrysin is associated with the inhiation of the PI3K/Akt and NF-κB pathways in melanoma. Chrysin decreases melanoma cell migration via the downregulation of the EMT-related proteins, E-cadherin, Snail and Smad; WNT/β-catenin target proteins, such as MMP2, MMP9, and VEGF have also been found to be downregulated by chrysin in melanoma cells (104) (Table III and Fig. 3). To overcome drug resistance in melanoma cells, nano-chrysin and nano-curcumin previous research used for the treatment of C57B16 mice bearing B16F10 melanoma tumors. It was observed that the combination of the two in an encapsulated form decreased the migration of these highly metastatic cancer cells via the downregulation of MMPs, tissue inhibitor of metalloproteases and hTERT gene expression, more so in the mouse B16F10 melanoma tumor model (3,105) (Table II).

10. Chrysin in bladder cancer

Bladder cancer is another main type of cancer found in progressive countries. Its incidence rate is 6 lakh and >2 lakh deaths yearly according to the GLOBOCAN report in 2020 (106). As all conventional therapies are toxic and bladder cancer has exhibited resistance to chemotherapeutics, research is being conducted to discover and develop new strategies (107). Plant-derived bioactive compounds are being used for the treatment and prevention of different types of cancer, including bladder cancer (4,9,107). Notably, bladder cell cancer development is aided by the activation of AKT/ERK/PI3K and STAT (108-110). Chrysin has been shown to modulate the AKT pathway in bladder fibrosis (111) (Fig. 3). Chrysin is a phytochemical found in honey and bee propolis and it causes increase in ROS leading to upregulation of caspases, downregulation of Bcl2, Bcl-xL and inhibition of STAT3 and Mcl-1 (112). Chrysin promotes the apoptosis of bladder cancer cells (T-24 and 5637) via the upregulation of caspase-9 and -3, and the downregulation of Bcl-xL, Mcl-1 and Bcl-2 and the intrinsic pathway (112) (Table IV).

The mutation of TP53 is the main reason for the poor survival rates of patients with bladder cell cancer. Chrysin inhibits the propagation of bladder cancer cells having mutated and wild-type TP53. Chrysin increases in reactive oxygen species, halts the cell cycle, and promotes the downregulation of SRC, PLK1 and HOXB3 in cells having mutated. Chrysin also promotes DNA hypermethylation in grade 2 cells, and downregulates mTOR and c-MYC in grade 3 cells. It has been proven that chrysin activity is related to the TP53 status (113,114). The combined use of chrysin with other chemotherapeutics exerts a synergistic effect. A previous study demonstrates that the combination of TRAIL and chrysin led to a decrease in the resistance of bladder cells to treatment and increased cell death (115).

11. Chrysin in hepatocellular carcinoma

The effects of chrysin in hepatocellular carcinoma have been reported by various studies (Table IV). Among the different factors that affect cancer cell metabolism, namely the change from oxidative phosphorylation to aerobic glycolysis, hexokonase2 is a key protein (116). Chrysin revokes the initial development of hepatic cancer and encourages programmed cell death in N-nitroso-diethylamine-created early neoplastic lumps in rats (117). In a previous study, Chrysin decreased expression of HK-2 in mitochondria, and the interaction between HK-2 and VDAC 2 was disrupted, which resulted in a marked increase in membrane permeability and the release of pro-apoptotic enzymes, such as cytochrome *c* and the release of Bax in hepatocellular carcinoma cells and animal models (118). As previously demonstrated, by decreasing the expression of specified hexokinase2, chrysin decreased glucose absorption and lactate generation in hepatocellular carcinoma cells and apoptosis was induced by chrysin due to the translocation of Bax from the cytoplasm to the mitochondria. Furthermore, in hepatocellular carcinoma xenograft models, Chrysin resulted in a promising decrease in tumor development via hexokinase-2 downregulation (118). Chrysin exerted its effect on propagation and programmed cell death in diethyl nitrosamine-induced early hepatocarcinogenesis in male Wistar rats. COX-2, NF-κB p65 and BcL-xL downregulation was observed, and Bax, p53 and caspase-3 exhibited an amplified expression (117).

The emergence of chemoresistance has been linked to the constitutive activation of the Nrf2-mediated signaling pathway. Gao *et al* (119) examined whether Nrf2 expression was connected to drug resistance in BEL-7402 (BEL-7402/ADM) cells that were resistant to doxorubicin, and whether chrysin could reverse drug resistance in BEL-7402/ADM cells. It was observed that chrysin markedly decreased Nrf2 expression at both the mRNA and protein level via the downregulation of the PI3K-Akt and ERK pathways (119). In another study, the combination of chrysin and curcumin led to the apoptosis of HepG2 cells via the p53 pathway (120) (Table II).

12. Chrysin in gastric cancer

Gastric cancer is placed fifth for frequency and fourth for mortality globally, and an estimated 769,000 deaths have been recorded according to the GLOBOCAN report in 2020) (106). Conventional therapies are unable to entirely cure cancer or considerably enhance the quality of life of patients with cancer metastasis due to cancer cell migration.

Table IV. The concentrations/doses of chrysin in hepatocellular and bladder cancer cells/animal models.

Authors, year of publication	Cancer type	Cell line/animal model	Concentration/dose	Mechanism of action	(Refs.)
Xu *et al*, 2018	Bladder cancer	T-24 and 5637	20-80 μM	Chrysin is significantly cytotoxic against bladder cancer cells as compared to normal bladder cells SV-HUC-1.	(112)
Lima *et al*, 2020	Bladder Cancer	10, 20, 40, 60 80 and 100 μM	10, 20, 40, 60 80 and 100 μM	Chrysin also stimulated DNA hypermethylation in grade 2 cells, and downregulated c-MYC, FGFR3 and mTOR gene in grade 3 cells.	(113)
Khan *et al*, 2011	Hepatocarcinogenesis	Diethyl nitrosamine (DEN)-induced cancer male Wistar rats.	Chrysin 250 mg/kg B.W.	Chrysin induced apoptosis by upregulation of p53, caspase-3 and Bax\downregulation of Bcl-xL.	(117)
Zhang *et al*, 2016	Hepatocellular carcinoma	HepG2 and QGY7701 c	10-80 μg/ml	p53/Bcl2/caspase-9 pathway led apoptosis.	(39)
Xu *et al*, 2017	Hepatocellular cancer	HepG2, Hep3B, Huh-7, SMMC-7721, Bel-7402 and athymic nude mice injected HCC-LM3	15-60 μM/30 mg/Kg B. W.	Chrysin led to downregulation of Hex2, suppression of anaerobic glycolysis and induction of apoptosis.	(118)
Khan *et al*, 2011	Hepatocellular cancer	N-nitrosodiethylamine (DEN) induced hepatocarcinoma in Wistar rats.	Oral dose of 250 mg/kg B.W	Chrysin inhibited cell proliferation, instigated apoptosis, and induction of global hepato-protective effect. Chemopreventive activity is related with p53-mediatedapoptosis during early hepatocarcinogenesis.	(117)

Table V. The concentrations/doses of chrysin in gastric and colon/colorectal cancer cells/animal models.

Authors, year of publication	Cancer type	Cell line/animal model	Concentration dosage	Mechanism of action	(Refs.)
Xia *et al*, 2015	Gastric cancer	AGS cell	0 to 100 μM	Chrysin depresses MMP-9 by blocking the JNK1/2 and ERK1/2 pathways in gastric cancer AGS cells	(122)
Xia *et al*, 2015	Gastric cancer	AGS cells	0 to 100 μM	Chrysin suppresses RON expression through blocking Egr-1 and NF-κB.	(121)
Zhong *et al*, 2020	Gastric cancer	Cell lines MKN-45/ MKN-45 injected into nude mice	40 μM/20 mg/kg B.W for 2 weeks	Chrysin shows anti-growth and anti-migratory regulation of TET1.	(123)
Mohammadian *et al*, 2017	Gastric cancer	AGS cells	0 to 160 μM	Chrysin alters microRNAs expression, let 7 and miR 9 upregulated and mir 18, miR21 and miR221 were downregulated.	(126)
Mohammadian *et al*, 2016	Gastric Cancer	AGS cells	0 to 160 μM	PLGA-PEG-chrysin complex nanoparticles significantly decrease miR-18a, miR-21, and miR- 221 mRNA gene expression.	(128)
Mohammadian *et al*, 2017	Gastric Cancer	AGS cells	0 to 160 μM	Upregulation of miR-9 and Let-7a by Nano encapsulated chrysin in gastric. cancer cell.	(129)
Zhang *et al*, 2016	Colon cancer cells	HT-55, HCA-7, and LoVo and CCD 841 CoTr human colon cells	0.01 to 10 mM	Chrysin decreased viability of HT-55, HCA7 and LoVo cancer cells /no cytotoxicity on normal colon cells.	(130)
Bahadori *et al*, 2016	Colon cancer cells	CT26 cell line/ CT26 tumor cells in Male BALB/c mice	0.5 to 10 mg/Kg B.W for 2 weeks	4, 8, 10 mg.kg-1 reduces the tumor volume in Balb mice.	(38)
Song *et al*, 2019	Colon cancer cells	H29	Irradiated chrysin (1 mg/kg. B.W)	Gamma irradiated chrysin showed profound apoptotic effect in HT-29 cells than undamaged chrysin.	(131)
Lin *et al*, 2018	Colorectal cells	SW480, HT29, HCT116	5-50 chrysin/5-FU + oxaliplatin (10, 25 μM)	Chrysin induces cytotoxicity comparable to combination of oxaliplatin and 5-FU.	(134)

As a result, innovative medicines that target the abnormal pathways that contribute to cancer invasion or metastasis are being developed (121). Chrysin has been shown to exert significant effects in gastric cancer (Table V). Chrysin has been shown to suppress both endogenous and inducible recepteur d'origine nantais (RON), expression dose-dependently. The transcription factors, Egr-1 and NF-κB, have a significant function in RON activity. Furthermore, by inhibiting Egr-1 and NF-κB in AGS cells, chrysin reduces RON expression at both levels (121) (Fig. 3). Chrysin instigated the movement of gastric cancer cells via the downregulation of MMP9 and the downregulation of JNK and ERK pathways (122). In gastric cancer (MKN45) cells, the effect of chrysin on the expression profile of TET proteins (TET1-3) was recently investigated. TET enzymes play a role in DNA demethylation and, as a result, alter gene expression via epigenetic mechanisms. It was found that TET1 expression in gastric cancer cells was enhanced by chrysin exposure at both the transcript and protein levels. Chrysin, a HDAC inhibitor, caused cytotoxicity, and also inhibited migration and invasion. These effects were discovered to be mediated by TET1 overexpression induced by chrysin. TET1 overexpression in gastric cancer cells replicated Chrysin-induced actions, leading to this result. Notably, chrysin treatment induced apoptosis via the modulation of Bax/Bcl-2, caused cell cycle detention at the sub G1 phase and repressed the metastasis of MKN-45 cells. In animal experiments, chrysin decreased cancer development and increased TET1 expression. Chrysin administration (20 mg/kg) for 14 days significantly attenuated tumor development in a nude mouse xenograft model of gastric cancer (123). These results demonstrate that chrysin promotes programmed cell death in gastric cancer cells initiated by the epigenetic player, TET1 (42). Furthermore, dysregulation in miRNA expression leads to the appearance of pathological circumstances, particularly cancer (124,125). Mohammadian *et al* (126) reported that chrysin upregulated miR-9 and miR 22, and decreased miR-18, miR-21 and miR-221 expression in the AGS cell line (Table V). The use of chrysin and PLGA-PEG nanoparticles has been shown to lead to the greater promotion of miR-34a, miR-126 and miR-22 gene expression, in comparison with free chrysin (127). In another study, the greater decrease of miR-18a, miR-21 and miR-221 was attained by chrysin-loaded PLGA-PEG nanoparticles (128). A previous study demonstrated that chrysin upregulated miR-9 and Let-7a as onco-suppressor aspects in cancer to hinder the propagation of gastric cancer cells. Nanoparticles suggestively encourage the aptitude of chrysin in upregulating miR-9 expression (129). It has been found that chrysin with other chemotherapeutic agents enhances the anticancer effect. The synergistic effect of chrysin and 5-fluorouracil (5-FU) (Table II) was observed in AGS/5-FU-resistant AGS cells with an enhanced p53-p21 activity, with the arrest of the cell cycle at the G2/M phase (43). Chrysin and cisplatin used concomitantly have been shown to lead to the self-programmed death of HepG2 cells via both extracellular signals and mitochondrial pathways by the activation of respective caspases) (120) (Table II). Chrysin has also been shown to enhance the sensitivity of BEL-7402/ADM cells to doxorubicin (121).

13. Chrysin in colorectal cancer

Colorectal cancer (CRC) is ranked third in terms of frequency, but second in terms of cancer-related mortality. The incidence rates are ~4-fold greater in developed countries than in developing ones. The colon cancer incidence rates vary by ~9-fold throughout the globe, with the highest rates observed in Europe, New Zealand and North America, with a higher incidence in the male population. However, Norway and Hungary also exhibit the highest rates, although the incidence here among males and females is equal (106). Previously, in *in vitro* and *in vivo* experiments, the cytotoxic effects of chrysin (Table V) and its line of action were verified in colon cancer cells (CT26) (38). Chrysin exerted cytotoxic effects and induced the apoptosis of CT26 cells in a concentration-dependent manner (IC50, 80 μg/ml). Furthermore, Chrysin-treated mice exhibited a considerable reduction in tumor volume (38). A marked reduction in the colon tumor volume in treated mice (8 and 10 mg/kg) was observed as compared to the untreated mice. RT-PCR elucidated that chrysin attenuated the tumor volume through the downregulation of the Sall4 and the upregulation of Bax. Thus, the downregulation of Sall4 and the increased expression of Bax were linked to a decreased tumor volume (38). The anticancer activity of chrysin has also been investigated in studies involving the colon cancer cell lines, HT-55, HCA-7 and LoVo. The IC50 values of chrysin against these cell lines ranged from 0.4 to 0.8 mM with the modulation of various molecules, such as ERK and AKT (42,130). Another study found that irradiated chrysin induced the intrinsic apoptosis of H29 colon cancer cells (131).

Chrysin in combination with other chemotherapeutic agents has exhibited notable results. Drug resistance and adverse effects have limited the use of 5-FU in the treatment of patients with CRC (132,133). In the treatment of CRC, chrysin has recently been proposed as a substitute for 5-FU. The use of chrysin (5-50 M) has been linked to a considerable reduction in the viability of CRC cells (134). Autophagy is influenced by chrysin in the treatment if CRC, according to a study of the molecular processes. Autophagy is a 'self-digestion' process that is triggered by stressful situations, such endoplasmic reticulum stress, mitochondrial injury, malnutrition, etc. (135). Curcumin- and chrysin-loaded PLGA-PEG nanoparticles have been shown to exert a collaborative effect and improve the cell death effects of these bioactive agents against colorectal cancer cells (136). A previous study demonstrated that apigenin used in combination with chrysin suppressed the development and migration of CRC cells by reducing p38-MAPK/AKT activity; however, at higher doses of chrysin (50 and 100 μM), the effect was antagonistic (137) (Table II).

Nanoparticle-based combinatorial chemotherapy has been proposed as a potential technique for increasing intracellular drug concentrations and achieving synergistic effects in anticancer therapy. It has been shown that chrysin and curcumin alone exert a dose-dependent cytotoxic effect on Caco-2 cells (138). However, curcumin-chrysin-loaded nanoparticles, on the other hand, exert a significant inhibitory effect on proliferation in comparison to the drugs used alone, leading to a marked decrease in hTERT expression (138). Nano-encapsulated chrysin and curcumin exert have been shown to exert a high synergistic effect on SW480 cells cancer

cells, as compared to their free versions. The SW480 CRC cells subjected to a combination of chrysin and curcumin in a nano-encapsulated form were found to exhibit a significant inhibition of hTERT expression (136) (Fig. 5).

14. Chrysin in ovarian cancer

Ovarian cancer is not often detected, but is a very fatal cancer and is the principal cause of mortality due to gynecological cancers (139). Ovarian cancer is divided into epithelial, germ cell, or stromal tumors, based upon their location within the ovary (140), with the most common being the epithelial type; this can be categorized into the benign, low malignant and malignant type (141). The treatment regimen for ovarian cancer is surgery followed by chemotherapy using carboplatin or cisplatin or a combination of the two (140). However, due to the side-effects associated with conventional therapies, it appears that plant-derived agents are probable candidates for the treatment and prevention ovarian cancer (40,142). Treatment with chrysin has been shown to lead to the induction of cell death and the intrinsic apoptosis of A2780cp cisplatin-resistant human ovarian cancer cells (143). Another study demonstrated that the treatment of ovarian cancer cells with chrysin led to an upsurge in the concentration of ROS and cytoplasmic Ca^{2+} and the activation of the MAPK/PI3K pathways, that resulted in the induction of self-programed cell death (40). However, by contrast, a number of studies have demonstrated that the activation of the PI3K/AKT pathway contributes to cell proliferation and metastasis, and the inhibition of this pathway is a potential pathway for targeted cancer therapy (4,56,144). Thus, aforementioned study has depicted that chrysin suppresses ovarian cancer via the activation of PI3K/AKT and MAPK (40). Hence, further research is warranted in order to fully understand the exact modes of action of chrysin.

Additionally, it has been reported that there is an association between the incidence of cancer and diabetes (145); chrysin targets various disorders, including diabetes and cancer. However, o date, to the best of our knowledge, there are no data available demonstrating that the anti-diabetic action of chrysin has prevented the occurrence of cancer.

15. Conclusion and future prospects

In conclusion, researchers are currently focusing on finding the impact of various plant-derived agents on cancers with the aim of developing cancer therapies. The results of this research are aiding in the more in-depth understanding of the causes and development of cancer. Although the effects of chrysin have been shown in various types of cancer, the exact molecular mechanisms through which chrysin controls the progression of different types of cancer have not yet been fully eludicated. Nevertheless, the majority of the data presented to date validate the effects of chrysin on various types of cancer *in vitro* and in animal models. However, the use of chrysin as a therapeutic agent in clinical setups is still far from being realized, until trials on humans are not performed and validated. In addition, experiments to confirm its effects in combination with conventional treatment agents and to enhance the treatment efficacy are required.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

RR and AH were involved in the design of the study and in the literature search for relevant references. RB edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hsieh YS, Yang SF, Sethi G and Hu DN: Natural bioactives in cancer treatment and prevention. Biomed Res Int 2015: 182835, 2015.
2. Montané X, Kowalczyk O, Reig-Vano B, Bajek A, Roszkowski K, Tomczyk R, Pawliszak W, Giamberini M, Mocek-Płóciniak A and Tylkowski B: Current perspectives of the applications of polyphenols and flavonoids in cancer therapy. Molecules 25: 3342, 2020.
3. Raina R, Hussain A and Sharma R: Molecular insight into apoptosis mediated by flavones in cancer (review). World Acad Sci J 2: 6, 2020.
4. Raina R, Afroze N, Sundaram MK, Haque S, Bajbouj K, Hamad M and Hussain A: Chrysin inhibits propagation of HeLa cells by attenuating cell survival and inducing apoptotic pathways. Eur Rev Med Pharmacol Sci 25: 2206-2220, 2021.
5. Muthusami S, Prabakaran DS, An Z, Yu JR and Park WY: EGCG suppresses fused toes homolog protein through p53 in cervical cancer cells. Mol Biol Rep 40: 5587-5596, 2013.
6. Pratheeshkumar P, Sreekala C, Zhang Z, Budhraja A, Ding S, Son YO, Wang X, Hitron A, Hyun-Jung K, Wang L, *et al*: Cancer prevention with promising natural products: Mechanisms of action and molecular targets. Anticancer Agents Med Chem 12: 1159-1584, 2012.
7. Kasala ER, Bodduluru LN, Barua CC, Madhana RM, Dahiya V, Budhani MK, Mallugari RR, Maramreddy SR and Gogoi R: Chemopreventive effect of chrysin, a dietary flavone against benzo(a)pyrene induced lung carcinogenesis in Swiss albino mice. Pharmacol Rep 68: 310-318, 2016.
8. Singh P, Tomar RS and Rath SK: Anticancer potential of the histone deacetylase inhibitor-like effects of flavones, a subclass of polyphenolic compounds: A review. Mol Biol Rep 42: 1515-1531, 2015.
9. Abdal Dayem A, Choi HY, Yang GM, Kim K, Saha SK and Cho SG: The anti-cancer effect of polyphenols against breast cancer and cancer stem cells: Molecular mechanisms. Nutrients 8: 581, 2016.

10. Kasala ER, Bodduluru LN, Madana RM, V AK, Gogoi R and Barua CC: Chemopreventive and therapeutic potential of chrysin in cancer: Mechanistic perspectives. Toxicol Lett 233: 214-225, 2015.
11. Sak K: Characteristic features of cytotoxic activity of flavonoids on human cervical cancer cells. Asian Pacific J Cancer Prev 15: 8007-8019, 2014.
12. Zhou Y, Zheng J, Li Y, Xu DP, Li S, Chen YM and Li H: Natural polyphenols for prevention and treatment of cancer. Nutrients 8: 515, 2016.
13. Wu X, Li M, Xiao Z, Daglia M, Dragan S, Delmas D, Vong T, Wang Y, Zhao Y, Shen J, *et al*: Dietary polyphenols for managing cancers: What have we ignored? Trends Food Sci Technol 101: 150-164, 2020.
14. Kopustinskiene DM, Jakstas V, Savickas A and Bernatoniene J: Flavonoids as anticancer agents. Nutrients 12: 457, 2020.
15. Selvakumar P, Badgeley A, Murphy P, Anwar H, Sharma U, Lawrence K and Lakshmikuttyamma A: Flavonoids and other polyphenols act as epigenetic modifiers in breast cancer. Nutrients 12: 761, 2020.
16. Bodduluru LN, Kasala ER, Thota N, Barua CC, Sistla R, Bodduluru LN, *et al*: Chemopreventive effect of chrysin, a dietary flavone against benzo(a)pyrene induced lung carcinogenesis in Swiss albino mice. Pharmacol Rep 68: 310-318, 2016.
17. Ramírez-Espinosa JJ, Saldaña-Ríos J, García-Jiménez S, Villalobos-Molina R, Ávila-Villarreal G, Rodríguez-Ocampo AN, Bernal-Fernández G and Estrada-Soto S: Chrysin induces antidiabetic, antidyslipidemic and anti-inflammatory effects in athymic nude diabetic mice. Molecules 23: 67, 2017.
18. Naz S, Imran M, Rauf A, Orhan IE, Shariati MA, Iahtisham-Ul-Haq, IqraYasmin, Shahbaz M, Qaisrani TB, Shah ZA, *et al*: Chrysin: Pharmacological and therapeutic properties. Life Sci 235: 116797, 2019.
19. Balta C, Herman H, Boldura OM, Gasca I, Rosu M, Ardelean A and Hermenean A: Chrysin attenuates liver fibrosis and hepatic stellate cell activation through TGF-β/Smad signaling pathway. Chem Biol Interact 240: 94-101, 2015.
20. Tsuji PA and Walle T: Cytotoxic effects of the dietary flavones chrysin and apigenin in a normal trout liver cell line. Chem Biol Interact 171: 37-44, 2008.
21. Talebi M, Talebi M, Farkhondeh T, Simal-Gandara J, Kopustinskiene DM, Bernatoniene J and Samarghandian S: Emerging cellular and molecular mechanisms underlying anticancer indications of chrysin. Cancer Cell Int 21: 214, 2021.
22. Galijatovic A, Otake Y, Walle UK and Walle T: Extensive metabolism of the flavonoid chrysin by human Caco-2 and Hep G2 cells. Xenobiotica 29: 1241-1256, 1999.
23. Ge S, Gao S, Yin T and Hu M: Determination of pharmacokinetics of chrysin and its conjugates in wild-type FVB and Bcrp1 knockout mice using a validated LC-MS/MS method. J Agric Food Chem 63: 2902-2910, 2015.
24. Lee JA, Jung BG, Kim TH, Kim YM, Park MH, Hyun PM, Jeon JW, Park JK, Cho CW, Suh GH and Lee BJ: Poly D,L-lactide-co-glycolide (PLGA) nanoparticle-encapsulated honeybee (Apis melifera) venom promotes clearance of Salmonella enterica serovar Typhimurium infection in experimentally challenged pigs through the up-regulation of T helper type 1 specific immune responses. Vet Immunol Immunopathol 161: 193-204, 2014.
25. Arafa MG, Ghalwash D, El-Kersh DM and Elmazar MM: Propolis-based niosomes as oromuco-adhesive films: A randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers. Sci Rep 8: 18056, 2018.
26. Mohammadinejad S, Akbarzadeh A, Rahmati-Yamchi M, Hatam S, Kachalaki S, Zohreh S and Zarghami N: Preparation and evaluation of chrysin encapsulated in PLGA-PEG nanoparticles in the T47-D breast cancer cell line. Asian Pacific J Cancer Prev 16: 3753-3758, 2015.
27. Brown GA, Martini ER, Kohut ML, Franke WD, Jackson DA, King DS and King DS: Endocrine and lipid responses to chronic androstenediol-herbal supplementation in 30 to 58 year old men. J Am Coll Nutr 20: 520-528, 2001.
28. Moghadam ER, Ang HL, Asnaf SE, Zabolian A, Saleki H, Yavari M, Esmaeili H, Zarrabi A, Ashrafizadeh M and Kumar AP: Broad-spectrum preclinical antitumor activity of chrysin: Current trends and future perspectives. Biomolecules 10: 1374, 2020.
29. Slominski RM, Raman C, Chen JY and Slominski AT: How cancer hijacks the body's homeostasis through the neuroendocrine system. Trends Neurosci 46: 263-275, 2023.
30. Mishra A, Mishra PS, Bandopadhyay R, Khurana N, Angelopoulou E, Paudel YN and Piperi C: Neuroprotective potential of chrysin: Mechanistic insights and therapeutic potential for neurological disorders. Molecules 26: 6456, 2021.
31. El-Sisi AE, El-Sayad ME and Abdelsalam NM: Protective effects of mirtazapine and chrysin on experimentally induced testicular damage in rats. Biomed Pharmacother 95: 1059-1066, 2017.
32. El-Bassossy HM, Abo-Warda SM and Fahmy A: Chrysin and luteolin attenuate diabetes-induced impairment in endothelial-dependent relaxation: Effect on lipid profile, AGEs and NO generation. Phyther Res 27: 1678-1684, 2013.
33. Satyanarayana K, Sravanthi K, Shaker I, Ponnulakshmi R and Selvaraj J: Role of chrysin on expression of insulin signaling molecules. J Ayurveda Integr Med 6: 248-258, 2015.
34. Samarghandian S, Farkhondeh T and Azimi-Nezhad M: Protective effects of chrysin against drugs and toxic agents. Dose Response 15: 1559325817711782, 2017.
35. Mantawy EM, El-Bakly WM, Esmat A, Badr AM and El-Demerdash E: Chrysin alleviates acute doxorubicin cardiotoxicity in rats via suppression of oxidative stress, inflammation and apoptosis. Eur J Pharmacol 728: 107-118, 2014.
36. Tahir M and Sultana S: Chrysin modulates ethanol metabolism in Wistar rats: A promising role against organ toxicities. Alcohol Alcohol 46: 383-392, 2011.
37. Raina R, Almutary AG, Bagabir SA, Afroze N, Fagoonee S, Haque S and Hussain A: Chrysin modulates aberrant epigenetic variations and hampers migratory behavior of human cervical (HeLa) cells. Front Genet 12: 768130, 2022.
38. Bahadori M, Baharara J and Amini E: 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: 177-184, 2016.
39. Zhang Q, Ma S, Liu B, Liu J, Zhu R and Li M: Chrysin induces cell apoptosis via activation of the p53/Bcl-2/caspase-9 pathway in hepatocellular carcinoma cells. Exp Ther Med 12: 469-474, 2016.
40. Lim W, Ryu S, Bazer FW, Kim SM and Song G: Chrysin attenuates progression of ovarian cancer cells by regulating signaling cascades and mitochondrial dysfunction. J Cell Physiol 233: 3129-3140, 2018.
41. Zaric M, Mitrovic M, Nikolic I, Baskic D, Popovic S, Djurdjevic P, Milosavljevic Z and Zelen I: Chrysin induces apoptosis in peripheral blood lymphocytes isolated from human chronic lymphocytic leukemia. Anticancer Agents Med Chem 15: 189-195, 2015.
42. Ganai SA, Sheikh FA and Baba ZA: Plant flavone chrysin as an emerging histone deacetylase inhibitor for prosperous epigenetic-based anticancer therapy. Phyther Res 35: 823-834, 2021.
43. Lee S, Lee SK and Jung J: Potentiating activities of chrysin in the therapeutic efficacy of 5-fluorouracil in gastric cancer cells. Oncol Lett 21: 24, 2021.
44. Liu Y, Xie S, Wang Y, Luo K, Wang Y and Cai Y: Liquiritigenin inhibits tumor growth and vascularization in a mouse model of HeLa cells. Molecules 17: 7206-7216, 2012.
45. Jin YM, Xu TM, Zhao YH, Wang YC and Cui MH: In vitro and in vivo anti-cancer activity of formononetin on human cervical cancer cell line HeLa. Tumor Biol 35: 2279-2284, 2014.
46. Hussain A, Harish G, Prabhu SA, Mohsin J, Khan MA, Rizvi TA and Sharma C: Inhibitory effect of genistein on the invasive potential of human cervical cancer cells via modulation of matrix metalloproteinase-9 and tissue inhibitiors of matrix metalloproteinase-1 expression. Cancer Epidemiol 36: e387-e393, 2012.
47. Chou RH, Hsieh SC, Yu YL, Huang MH, Huang YC and Hsieh YH: Fisetin inhibits migration and invasion of human cervical cancer cells by down-regulating urokinase plasminogen activator expression through suppressing the p38 MAPK-dependent NF-κB signaling pathway. PLoS One 8: e71983, 2013.
48. Chen YJ, Kay N, Yang JM, Lin CT, Chang HL, Wu YC, Fu CF, Chang Y, Lo S, Hou MF, *et al*: Total synthetic protoapigenone WYC02 inhibits cervical cancer cell proliferation and tumour growth through PIK3 signalling pathway. Basic Clin Pharmacol Toxicol 113: 8-18, 2013.
49. Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah ASV, McAllister DA, Gottlieb SL, Klug SJ, Winkler AS, *et al*: Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health 9: e161-e169, 2021.

50. Ham S, Kim KH, Kwon TH, Bak Y, Lee DH, Song YS, Park SH, Park YS, Kim MS, Kang JW, *et al*: Luteolin induces intrinsic apoptosis via inhibition of E6/E7 oncogenes and activation of extrinsic and intrinsic signaling pathways in HPV-18-associated cells. Oncol Rep 31: 2683-2691, 2014.
51. Kim MS, Bak Y, Park YS, Lee DH, Kim JH, Kang JW, Song HH, Oh SR and Yoon DY: Wogonin induces apoptosis by suppressing E6 and E7 expressions and activating intrinsic signaling pathways in HPV-16 cervical cancer cells. Cell Biol Toxicol 29: 259-272, 2013.
52. Garcia FAR, Cornelison T, Nuño T, Greenspan DL, Byron JW, Hsu CH, Alberts DS and Chow HH: Results of a phase II randomized, double-blind, placebo-controlled trial of Polyphenon E in women with persistent high-risk HPV infection and low-grade cervical intraepithelial neoplasia. Gynecol Oncol 132: 377-382, 2014.
53. Cherry JJ, Rietz A, Malinkevich A, Liu Y, Xie M, Bartolowits M, Davisson VJ, Baleja JD and Androphy EJ: Structure based identification and characterization of flavonoids that disrupt human papillomavirus-16 E6 function. PLoS One 8: e84506, 2013.
54. Berman TA and Schiller JT: Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. Cancer 123: 2219-2229, 2017.
55. Yin KB: Chrysin in PI3K/AKT and other apoptosis signalling pathways, and its effect on HeLa cells, 2014.
56. Khoo BY, Chua SL and Balaram P: Apoptotic effects of chrysin in human cancer cell lines. Int J Mol Sci 11: 2188-2199, 2010.
57. von Brandenstein MG, Abety AN, Depping R, Roth T, Koehler M, Dienes HP and Fries JWU: A p38-p65 transcription complex induced by endothelin-1 mediates signal transduction in cancer cells. Biochim Biophys Acta 1783: 1613-1622, 2008.
58. Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Athikomkulchai S, Viriyaroj A, Awale S, Ruchirawat S, Svasti J and Saiki I: Chrysin overcomes TRAIL resistance of cancer cells through Mcl-1 downregulation by inhibiting STAT3 phosphorylation. Int J Oncol 43: 329-337, 2013.
59. Kanwal R, Datt M, Liu X and Gupta S: Dietaryflavones as dual inhibitors of DNA methyltransferases and histone methyltransferases. PLoS One 11: e0162956, 2016.
60. Dong W, Chen A, Cao X, Li X, Cui YH, Xu C, Cao J and Ning Y: Chrysin inhibits proinflammatory factor-induced EMT phenotype and cancer stem cell-like features in HeLa cells by blocking the NF-κB/Twist axis. Cell Physiol Biochem 52: 1236-1250, 2019.
61. Pawar JS, Mustafa S and Ghosh I: Chrysin and Capsaicin induces premature senescence and apoptosis via mitochondrial dysfunction and p53 elevation in Cervical cancer cells. Saudi J Biol Sci 29: 3838-3847, 2022.
62. Raina R, Hussain A, Almutary AG, Haque S, Raza T, D'Souza AC, Subramani S and Sajeevan A: Co-administration of chrysin and luteolin with cisplatin and topotecan exhibits a variable therapeutic value in human cancer cells, HeLa. ACS Omega 8: 41204-41213, 2023.
63. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A and Siegel RL: Breast cancer statistics, 2019. CA Cancer J Clin 69: 438-451, 2019.
64. Pandey K, An HJ, Kim SK, Lee SA, Kim S, Lim SM, Kim GM, Sohn J and Moon YW: Molecular mechanisms of resistance to CDK4/6 inhibitors in breast cancer: A review. Int J Cancer 145: 1179-1188, 2019.
65. Pandey PR, Young KH, Kumar D and Jain N: RNA-mediated immunotherapy regulating tumor immune microenvironment: Next wave of cancer therapeutics. Mol Cancer 21: 58, 2022.
66. Shanmugam MK, Ahn KS, Hsu A, Woo CC, Yuan Y, Tan KHB, Chinnathambi A, Alahmadi TA, Alharbi SA, Koh APF, *et al*: Thymoquinone inhibits bone metastasis of breast cancer cells through abrogation of the CXCR4 signaling axis. Front Pharmacol 9: 1294, 2018.
67. Liu L, Ahn KS, Shanmugam MK, Wang H, Shen H, Arfuso F, Chinnathambi A, Alharbi SA, Chang Y, Sethi G and Tang FR: Oleuropein induces apoptosis via abrogating NF-κB activation cascade in estrogen receptor-negative breast cancer cells. J Cell Biochem 120: 4504-4513, 2019.
68. Yang B, Huang J, Xiang T, Yin X, Luo X, Huang J, Luo F, Li H, Li H and Ren G: 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: 105-112, 2014.
69. Rasouli S and Zarghami N: Synergistic growth inhibitory effects of chrysin and metformin combination on breast cancer cells through hTERT and cyclin D1 suppression. Asian Pacific J Cancer Prev 19: 977-982, 2018.
70. Samarghandian S, Azimi-Nezhad M, Borji A, Hasanzadeh M, Jabbari F, Farkhondeh T and Samini M: Inhibitory and cytotoxic activities of Chrysin on human breast adenocarcinoma cells by induction of apoptosis. Pharmacogn Mag 12 (Suppl 4): S436-S440, 2016.
71. Sun LP, Chen AL, Hung HC, Chien YH, Huang JS, Huang CY, Chen YW and Chen CN: 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, 2012.
72. Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Maruyama T, Athikomkulchai S, Viriyaroj A, Awale S, Yagita H, Ruchirawat S, *et al*: A flavonoid chrysin suppresses hypoxic survival and metastatic growth of mouse breast cancer cells. Oncol Rep 30: 2357-2364, 2013.
73. Mohammadi Z, Sharif Zak M, Seidi K, Barati M, Akbarzadeh A and Zarghami N: The effect of chrysin loaded PLGA-PEG on metalloproteinase gene expression in mouse 4T1 tumor model. Drug Res (Stuttg) 67: 211-216, 2017.
74. Palakurthi S, Yellepeddi VK and Vangara KK: Recent trends in cancer drug resistance reversal strategies using nanoparticles. Expert Opin Drug Deliv 9: 287-301, 2012.
75. Javan Maasomi Z, Pilehvar Soltanahmadi Y, Dadashpour M, Alipour Sh, Abolhasani S and Zarghami N: Synergistic anticancer effects of silibinin and chrysin in T47D breast cancer cells. Asian Pacific J Cancer Prev 18: 1283-1287, 2017.
76. Roy S, Sil A and Chakraborty T: Potentiating apoptosis and modulation of p53, Bcl2, and Bax by a novel chrysin ruthenium complex for effective chemotherapeutic efficacy against breast cancer. J Cell Physiol 234: 4888-4909, 2019.
77. Sulaiman GM, Jabir MS and Hameed AH: Nanoscale modification of chrysin for improved of therapeutic efficiency and cytotoxicity. Artif Cells Nanomed Biotechnol 46 (Suppl 1): S708-S720, 2018.
78. Davaran S, Fazeli H, Ghamkhari A, Rahimi F, Molavi O, Anzabi M and Salehi R: Synthesis and characterization of novel P(HEMA-LA-MADQUAT) micelles for co-delivery of methotrexate and chrysin in combination cancer chemotherapy. J Biomater Sci Polym Ed 29: 1265-1286, 2018.
79. Anari E, Akbarzadeh A and Zarghami N: Chrysin-loaded PLGA-PEG nanoparticles designed for enhanced effect on the breast cancer cell line. Artif Cells Nanomed Biotechnol 44: 1410-1416, 2016.
80. Javan N, Khadem Ansari MH, Dadashpour M, Khojastehfard M, Bastami M, Rahmati-Yamchi M and Zarghami N: Synergistic antiproliferative effects of co-nanoencapsulated curcumin and chrysin on MDA-MB-231 breast cancer cells through upregulating miR-132 and miR-502c. Nutr Cancer 71: 1201-1213, 2019.
81. Shao JJ, Zhang AP, Qin W, Zheng L, Zhu YF and Chen X: AMP-activated protein kinase (AMPK) activation is involved in chrysin-induced growth inhibition and apoptosis in cultured A549 lung cancer cells. Biochem Biophys Res Commun 423: 448-453, 2012.
82. Zhang Y, Xu X, Li W, Miao H, Huang S, Zhou Y, Sun Y, Li Z, Guo Q and Zhao L: Activation of endoplasmic reticulum stress and the extrinsic apoptotic pathway in human lung cancer cells by the new synthetic flavonoid, LZ-205. Oncotarget 7: 87257-87270, 2016.
83. Pinsolle J, Terzi N, Ferrer L, Giaj Levra M, Toffart AC and Moro-Sibilot D: Les avancées dans la prise en charge des cancers bronchopulmonaires: Ce qui change pour le réanimateur. Méd Intensive Réa 28: 290-299, 2019.
84. Mehdi SH, Zafaryab M, Nafees S, Khan A, Ahmad I, Hafeez ZB and Rizvi MA: Chrysin sensitizes human lung cancer cells to tumour necrosis factor related apoptosis-inducing ligand (TRAIL) mediated apoptosis. Asian Pac J Cancer Biol 4: 27-33, 2019.
85. Maruhashi R, Eguchi H, Akizuki R, Hamada S, Furuta T, Matsunaga T, Endo S, Ichihara K and Ikari A: 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: 13753, 2019.
86. Lakshmi S, Suresh S, Rahul BS, Saikant R, Maya V, Gopi M, Padmaja G and Remani P: In vitro and in vivo studies of 5,7-dihydroxy flavones isolated from Alpinia galanga (L.) against human lung cancer and ascetic lymphoma. Med Chem Res 28: 39-51, 2019.
87. Samarghandian S, Azimi Nezhad M and Mohammadi G: Role of caspases, Bax and Bcl-2 in chrysin-induced apoptosis in the A549 human lung adenocarcinoma epithelial cells. Anticancer Agents Med Chem 14: 901-909, 2014.

88. Wu TC, Chan ST, Chang CN, Yu PS, Chuang CH and Yeh SL: Quercetin and chrysin inhibit nickel-induced invasion and migration by downregulation of TLR4/NF-κB signaling in A549 cells. Chem Biol Interact 292: 101-109, 2018.
89. Lim HK, Kim KM, Jeong SY, Choi EK and Jung J: Chrysin increases the therapeutic efficacy of docetaxel and mitigates docetaxel-induced edema. Integr Cancer Ther 16: 496-504, 2017.
90. Mohammad P, Nosratollah Z, Mohammad R, Abbas A and Javad R: The inhibitory effect of Curcuma longa extract on telomerase activity in A549 lung cancer cell line. Afr J Biotechnol 9: 912-919, 2010.
91. Brechbuhl HM, Kachadourian R, Min E, Chan D and Day BJ: Chrysin enhances doxorubicin-induced cytotoxicity in human lung epithelial cancer cell lines: The role of glutathione. Toxicol Appl Pharmacol 258: 1-9, 2012.
92. Shahbaz M, Naeem H, Imran M, Ul Hassan H, Alsagaby SA, Al Abdulmonem W, Waqar AB, Ghorab AH, Abdelgawad MA, Ghoneim MM, *et al*: Chrysin a promising anticancer agent: Recent perspectives. Int J Food Prop 26: 2294-2337, 2023.
93. Khazaei Z, Ghorat F, Jarrahi AM, Adineh HA, Sohrabivafa M and Goodarzi E: Global incidence and mortality of skin cancer by histological subtype and its relationship with the human development index (HDI); an ecology study in 2018 2018. World Cancer Res J 6: e1265, 2019.
94. Carr S, Smith C and Wernberg J: Epidemiology and risk factors of melanoma. Surg Clin North Am 100: 1-12, 2020.
95. Islam MM, Nagaraja S, Hafsa NE, Meravanige G, Asdaq SMB and Anwer MK: Polyphenol chrysin for management of skin disorders: Current status and future opportunities. J King Saud Univ Sci 34: 102026, 2022.
96. Sassi A, Maatouk M, El gueder D, Bzéouich IM, Abdelkefi-Ben Hatira S, Jemni-Yacoub S, Ghedira K and Chekir-Ghedira L: Chrysin, a natural and biologically active flavonoid suppresses tumor growth of mouse B16F10 melanoma cells: In vitro and in vivo study. Chem Biol Interact 283: 10-19, 2018.
97. Bittner M, Meltzer P, Chen Y, Jiang Y, Seftor E, Hendrix M, Radmacher M, Simon R, Yakhini Z, Ben-Dor A, *et al*: Molecular classification of cutaneous malignant melanoma by gene expression profiling. Nature 406: 536-540, 2000.
98. Slominski RM, Sarna T, Płonka PM, Raman C, Brożyna AA and Slominski AT: Melanoma, melanin, and melanogenesis: The Yin and Yang relationship. Front Oncol 12: 842496, 2022.
99. Slominski RM, Zmijewski MA and Slominski AT: The role of melanin pigment in melanoma. Exp Dermatol 24: 258-259, 2015.
100. Yang HZ, Zhang J, Zeng J, Liu S, Zhou F, Zhang F, Giampieri F, Cianciosi D, Forbes-Hernandez TY, Ansary J, *et al*: Resveratrol inhibits the proliferation of melanoma cells by modulating cell cycle. Int J Food Sci Nutr 71: 84-93, 2020.
101. Xue C, Chen Y, Hu D, Iacob C, Lu C and Huang Z: Chrysin induces cell apoptosis in human uveal melanoma cells via intrinsic apoptosis. Oncol Lett 12: 4813-4820, 2016.
102. Folgueras AR, Pendás AM, Sánchez LM and López-Otín C: Matrix metalloproteinases in cancer: From new functions to improved inhibition strategies. Int J Dev Biol 48: 411-424, 2004.
103. Chen HY, Jiang YW, Kuo CL, Way T Der, Chou YC, Chang YS and Chung JG: Chrysin inhibit human melanoma A375.S2 cell migration and invasion via affecting MAPK signaling and NF-κB signaling pathway in vitro. Environ Toxicol 34: 434-442, 2019.
104. Yufei Z, Yuqi W, Binyue H, Lingchen T, Xi C, Hoffelt D and Fuliang H: Chrysin Inhibits melanoma tumor metastasis via interfering with the FOXM1/β-catenin signaling. J Agric Food Chem 68: 9358-9367, 2020.
105. Tavakoli F, Jahanban-Esfahlan R, Seidi K, Jabbari M, Behzadi R, Pilehvar-Soltanahmadi Y and Zarghami N: Effects of nano-encapsulated curcumin-chrysin on telomerase, MMPs and TIMPs gene expression in mouse B16F10 melanoma tumour model. Artif Cells Nanomed Biotechnol 46 (Suppl 2): S75-S86, 2018.
106. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
107. Cai Z, Zhang F, Chen W, Zhang J and Li H: Mirnas: A promising target in the chemoresistance of bladder cancer. Onco Targets Ther 12: 11805-11816, 2019.
108. Korac-Prlic J, Degoricija M, Vilović K, Haupt B, Ivanišević T, Franković L, Grivennikov S and Terzić J: Targeting Stat3 signaling impairs the progression of bladder cancer in a mouse model. Cancer Lett 490: 89-99, 2020.
109. Sun N, Liang Y, Chen Y, Wang L, Li D, Liang Z, Sun L, Wang Y and Niu H: Glutamine affects T24 bladder cancer cell proliferation by activating STAT3 through ROS and glutaminolysis. Int J Mol Med 44: 2189-2200, 2019.
110. Anand V, Khandelwal M, Appunni S, Gupta N, Seth A, Singh P, Mathur S and Sharma A: CD44 splice variant (CD44v3) promotes progression of urothelial carcinoma of bladder through Akt/ERK/STAT3 pathways: Novel therapeutic approach. J Cancer Res Clin Oncol 145: 2649-2661, 2019.
111. Nagavally RR: Inhibition of epithelial mesenchymal transition (EMT) and renal fibrosis by chrysin involves modulation of Akt signaling. PhD dissertation. St. John's University (New York) ProQuest Dissertations & Theses. Publication no. 10170226, 2016. https://www.proquest.com/openview/9d262b69f271cffaa41ea9e6901fe3d0/1?pq-origsite=gscholar&cbl=18750.
112. Xu Y, Tong Y, Ying J, Lei Z, Wan L, Zhu X, Ye F, Mao P, Wu X, Pan R, *et al*: Chrysin induces cell growth arrest, apoptosis, and ER stress and inhibits the activation of STAT3 through the generation of ROS in bladder cancer cells. Oncol Lett 15: 9117-9125, 2018.
113. Lima APB, Almeida TC, Barros TMB, Rocha LCM, Garcia CCMH and Da Silva GN: Toxicogenetic and antiproliferative effects of chrysin in urinary bladder cancer cells. Mutagenesis 35: 361-371, 2020.
114. Talebi M, Talebi M, Kakouri E, Farkhondeh T, Pourbagher-Shahri AM, Tarantilis PA and Samarghandian S: Tantalizing role of p53 molecular pathways and its coherent medications in neurodegenerative diseases. Int J Biol Macromol 172: 93-103, 2021.
115. Szliszka E, Gebka J, Bronikowska J and Krol W: Dietary flavones enhance the effect of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on bladder cancer cells. Cent Eur J Urol 63: 138-143, 2010.
116. Guo-Qing P, Yuan Y, Cai-Gao Z, Hongling Y, Gonghua H and Yan T: A study of association between expression of hOGG1, VDAC1, HK-2 and cervical carcinoma. J Exp Clin Cancer Res 29: 129, 2010.
117. Khan MS, Devaraj H and Devaraj N: Chrysin abrogates early hepatocarcinogenesis and induces apoptosis in N-nitrosodiethylamine-induced preneoplastic nodules in rats. Toxicol Appl Pharmacol 251: 85-94, 2011.
118. Xu D, Jin J, Yu H, Zhao Z, Ma D, Zhang C and Jiang H: Chrysin inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexokinase-2. J Exp Clin Cancer Res 36: 44, 2017.
119. Gao AM, Ke ZP, Shi F, Sun GC and Chen H: Chrysin enhances sensitivity of BEL-7402/ADM cells to doxorubicin by suppressing PI3K/Akt/Nrf2 and ERK/Nrf2 pathway. Chem Biol Interact 206: 100-108, 2013.
120. Li X, Huang JM, Wang JN, Xiong XK, Yang XF and Zou F: Combination of chrysin and cisplatin promotes the apoptosis of Hep G2 cells by up-regulating p53. Chem Biol Interact 232: 12-20, 2015.
121. Xia Y, Lian S, Khoi PN, Yoon HJ, Han JY, Chay KO, Kim KK and Jung YD: Chrysin inhibits cell invasion by inhibition of recepteur d'origine Nantais via suppressing early growth response-1 and NF-κB transcription factor activities in gastric cancer cells. Int J Oncol 46: 1835-1843, 2015.
122. Xia Y, Lian S, Khoi PN, Yoon HJ, Joo YE, Chay KO, Kim KK and Do Jung Y: Chrysin inhibits tumor promoter-induced MMP-9 expression by blocking AP-1 via suppression of ERK and JNK pathways in gastric cancer cells. PLoS One 10: e0124007, 2015.
123. Zhong X, Liu D, Jiang Z, Li C, Chen L, Xia Y, Liu D, Yao Q and Wang D: Chrysin induced cell apoptosis and inhibited invasion through regulation of TET1 expression in gastric cancer cells. Onco Targets Ther 13: 3277-3287, 2020.
124. Wang J, Zhang L, Jiang W, Zhang R, Zhang B, Silayiding A and Duan X: MicroRNA-135a promotes proliferation, migration, invasion and induces chemoresistance of endometrial cancer cells. Eur J Obstet Gynecol Reprod Biol X 5: 100103, 2019.
125. Xu C, Li B, Zhao S, Jin B, Jia R, Ge J and Xu H: MicroRNA-186-5p inhibits proliferation and metastasis of esophageal cancer by mediating HOXA9. Onco Targets Ther 12: 8905-8914, 2019.
126. Mohammadian F, Pilehvar-Soltanahmadi Y, Alipour S, Dadashpour M and Zarghami N: Chrysin alters microRNAs expression levels in gastric cancer cells: Possible molecular mechanism. Drug Res (Stuttg) 67: 509-514, 2017.

127. Mohammadian F, Abhari A, Dariushnejad H, Nikanfar A, Pilehvar-Soltanahmadi Y and Zarghami N: Effects of chrysin-PLGA-PEG nanoparticles on proliferation and gene expression of miRNAs in gastric cancer cell line. Iran J Cancer Prev 9: e4190, 2016.
128. Mohammadian F, Pilehvar-Soltanahmadi Y, Mofarrah M, Dastani-Habashi M and Zarghami N: Down regulation of miR-18a, miR-21 and miR-221 genes in gastric cancer cell line by chrysin-loaded PLGA-PEG nanoparticles. Artif Cells Nanomed Biotechnol 44: 1972-1978, 2016.
129. Mohammadian F, Pilehvar-Soltanahmadi Y, Zarghami F, Akbarzadeh A and Zarghami N: Upregulation of miR-9 and Let-7a by nanoencapsulated chrysin in gastric cancer cells. Artif Cells Nanomed Biotechnol 45: 1-6, 2017.
130. Zhang MM, Huang SS, Long D and Lin X: Anti-proliferative action of chrysin in colon cancer cells and its effects on signaling pathways. Int J Clin Exp Med 9: 22784-22792, 2016.
131. Song HY, Kim HM, Mushtaq S, Kim WS, Kim YJ, Lim ST and Byun EB: Gamma-irradiated chrysin improves anticancer activity in HT-29 colon cancer cells through mitochondria-related pathway. J Med Food 22: 713-721, 2019.
132. Lee CS, Ryan EJ and Doherty GA: Gastro-intestinal toxicity of chemotherapeutics in colorectal cancer: The role of inflammation. World J Gastroenterol 20: 3751-3761, 2014.
133. Crea F, Nobili S, Paolicchi E, Perrone G, Napoli C, Landini I, Danesi R and Mini E: Epigenetics and chemoresistance in colorectal cancer: An opportunity for treatment tailoring and novel therapeutic strategies. Drug Resist Updat 14: 280-296, 2011.
134. Lin YM, Chen CI, Hsiang YP, Hsu YC, Cheng KC, Chien PH, Pan HL, Lu CC and Chen YJ: Chrysin attenuates cell viability of human colorectal cancer cells through autophagy induction unlike 5-fluorouracil/oxaliplatin. Int J Mol Sci 19: 1763, 2018.
135. Patra S, Mishra SR, Behera BP, Mahapatra KK, Panigrahi DP, Bhol CS, Praharaj PP, Sethi G, Patra SK and Bhutia SK: Autophagy-modulating phytochemicals in cancer therapeutics: Current evidences and future perspectives. Semin Cancer Biol 80: 205-217, 2022.
136. Bagheri R, Sanaat Z and Zarghami N: Synergistic effect of free and nano-encapsulated chrysin-curcumin on inhibition of hTERT gene expression in SW480 colorectal cancer cell line. Drug Res (Stuttg) 68: 335-343, 2018.
137. Zhang X, Zhang W, Chen F and Lu Z: Combined effect of chrysin and apigenin on inhibiting the development and progression of colorectal cancer by suppressing the activity of P38-MAPK/AKT pathway. IUBMB Life 73: 774-783, 2021.
138. Lotfi-Attari J, Pilehvar-Soltanahmadi Y, Dadashpour M, Alipour S, Farajzadeh R, Javidfar S and Zarghami N: Co-delivery of curcumin and chrysin by polymeric nanoparticles inhibit synergistically growth and hTERT gene expression in human colorectal cancer cells. Nutr Cancer 69: 1290-1299, 2017.
139. Casper AC, Parsons MW, Chipman J, Burt LM Jr, Suneja G, Maurer KA and Gaffney DK: Risk of secondary malignancies in ovarian cancer survivors: 52,680 Patients analyzed with over 40 years of follow-up. Gynecol Oncol 162: 454-460, 2021.
140. Jessmon P, Boulanger T, Zhou W and Patwardhan P: Epidemiology and treatment patterns of epithelial ovarian cancer. Expert Rev Anticancer Ther 17: 427-437, 2017.
141. Ulbright TM and Roth LM: Common epithelial tumors of the ovary: Proliferating and of low malignant potential. Semin Diagn Pathol 2: 2-15, 1985.
142. Guo X, Mei J, Jing Y and Wang S: Curcumin-loaded nanoparticles with low-intensity focused ultrasound-induced phase transformation as tumor-targeted and pH-sensitive theranostic nanoplatform of ovarian cancer. Nanoscale Res Lett 15: 73, 2020.
143. Amini E, Baharara J, Nikdel N and Abdollahi FS: Cytotoxic and pro-apoptotic effects of honey bee venom and chrysin on human ovarian cancer cells. Asia Pacific J Med Toxicol 4: 68-73, 2015.
144. Tewari D, Patni P, Bishayee A, Sah AN and Bishayee A: Natural products targeting the PI3K-Akt-mTOR signaling pathway in cancer: A novel therapeutic strategy. Semin Cancer Biol 80: 1-17, 2022.
145. Chang WC, Hsieh TC, Hsu WL, Chang FL, Tsai HR and He MS: Diabetes and further risk of cancer: A nationwide population-based study. BMC Med 22: 214, 2024.