Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org
Review

Regulation of cell signaling pathways by Schisandrin in different cancers: Opting for "Swiss Army Knife" instead of "Blunderbuss"

Xiukun Lin[1], Rukset Attar[2], Iqra Mobeen[3], Ishmuratova Margarita Yulaevna[4], Aliye Aras[5], Ghazala Butt[6*], Ammad Ahmad Farooqi[7*]

[1] Department of Pharmacology, Southwest Medical University, Luzhou, Sichuan, 646000 China
[2] Department of Obstetrics and Gynecology, Yeditepe University, Turkey
[3] Khursheed Rasheed Hospital Lahore, Pakistan
[4] E. A. Buketov Karaganda University, Kazakhstan
[5] Department of Botany, Faculty of Science, Istanbul University, Istanbul, Turkey
[6] Department of Botany, GCU, Lahore, Pakistan
[7] Department of Molecular Oncology, Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan

[*]**Correspondence to:** dr.ghazalayasmeen@gcu.edu.pk, Farooqiammadahmad@gmail.com

Received June 2, 2021; **Accepted** July 10, 2021; **Published** August 15, 2021

Doi: http://dx.doi.org/10.14715/cmb/2021.67.2.5

Abstract: There has been an exponential growth in the field of molecular oncology and cutting-edge research has enabled us to develop a better understanding of therapeutically challenging nature of cancer. Based on the mechanistic insights garnered from decades of research, puzzling mysteries of multifaceted nature of cancer have been solved to a greater extent. Our rapidly evolving knowledge about deregulated oncogenic cell signaling pathways has allowed us to dissect different oncogenic transduction cascades which play critical role in cancer onset, progression and metastasis. Pharmacological targeting of deregulated pathways has attracted greater than ever attention in the recent years. Henceforth, discovery and identification of high-quality biologically active chemicals and products is gaining considerable momentum. There has been an explosion in the dimension of natural product research because of tremendous potential of chemopreventive and pharmaceutical significance of natural products. Schisandrin is mainly obtained from *Schisandra chinensis*. Schisandrin has been shown to be effective against different cancers because of its ability to inhibit/prevent cancer via modulation of different cell signaling pathways. Importantly, regulation of non-coding RNAs by schisandrin is an exciting area of research that still needs detailed and comprehensive research. However, we still have unresolved questions about pharmacological properties of schisandrin mainly in context of its regulatory role in TGF/SMAD, SHH/GLI, NOTCH and Hippo pathways.

Key words: Cancer; Signaling; non-coding RNAs; Apoptosis; Metastasis.

Introduction

The efficacy of targeted therapies in patients with solid tumors is largely unpredictable mainly because of intrinsic genetic complexities and deregulation of oncogenic signaling pathways (1-3). Tireless efforts have been made by researchers worldwide to search for botanicals having significant pharmacological properties and minimal off-target effects (4-8).

Undoubtedly, natural products are a treasure trove for discovery of novel drugs and comprehensive analysis of plant extracts in the quest for medicinally valuable bioactive natural products is a gold-standard approach for the characterization of lead compounds in the drug discovery-derived research. Significant proportion of mainstream medicines has been obtained from natural sources. These landmark developments clearly indicate that natural products serve as excellent starting points in the design and development of new drug-like candidates. Therefore, when desired results are obtained from series of experiments, the next step is the isolation and analysis of the structures of the natural products responsible for the biological effects.

The genus Schisandra belongs to the family of Schisandraceae. Among several species, *Schisandra chinensis* Turcz. (Baill.) is a scientifically acclaimed plant having considerable hepatoprotective, neuroprotective, cardioprotective and anti-cancer effects. So far, many lignans have been obtained from *S. chinensis*. These lignans belong mostly to dibenzocyclooctane type. Deoxyschisandrin, schisandrin B, schisandrin C, schisantherin A, schisanthenol and gomisin are high-quality lignans having noteworthy pharmacologically valuable properties.

Schisandrin is an important biologically active product obtained from *Schisandra chinensis.* In this review, we have provided a summary of most recent experimental findings related to chemopreventive properties of schisandrin against different cancers. There are some good review articles published in this field related to its medicinal properties (9-12).

For the framework of the review, we have extensively browsed PubMed using different keywords particularly, "schisandrin and cancer", "schisandrin and

metastasis", "Schisandrin and signaling".

We have focused exclusively on schisandrin-mediated regulation of cell signaling pathways in different cancers. We have summarized how schisandrin modulated JAK/STAT and apoptotic pathways for cancer chemoprevention. Furthermore, we also provided a compendium of the regulation of protein networks by schisandrin in various cancers. Later, we have sketched a landscape of the anti-metastatic effects of schisandrin in tumor-bearing mice.

Role of STAT signaling

JAK/STAT signaling has been shown to play instrumental role in carcinogenesis (13-15).

Schisandrin B dose-dependently suppressed the levels of cyclin D1 and CDK4 (Cyclin-dependent kinase 4) in BT-549 and MDA-MB-231 cells (16). Schisandrin B reduced p-STAT3 levels in BT-549 and MDA-MB-231 cells (fig.1). STAT3 overexpression impaired Schisandrin B-induced apoptotic cell death in MDA-MB-231 cancer cells. Intraperitoneal injections of Schisandrin B induced regression of tumor mass in mice transplanted with MDA-MB-231 cancer cells (16).

MCF-7/DOX cells express high levels of MDR1. P-gp/MDR1 is transcriptionally upregulated by p-STAT3 and NF-κB (17). Schisandrin A selectively suppressed P-gp/MDR1 by blockade of p-STAT3 and NF-κB-mediated activation of P-gp (**fig**.1). Schisandrin A effectively suppressed the levels of p-STAT3 and p-IκB (17). Overall, these findings suggested that activation of STAT3 and NF-κB played central role in the development of resistance against different chemotherapeutic drugs.

Schisandrin B inhibited the phosphorylation of JAK2 and STAT3 in prostate LNCaP and DU145 cancer cells. Schisandrin B also downregulated the expression of androgen receptor in prostate cancer cells (18).

These findings indicated that schisandrin not only inhibited nuclear accumulation of STAT3 but also suppressed STAT3-mediated transcriptional regulation of target gene network. However, future studies must converge on the identification of additional pharmacological targets of schisandrin in JAK/STAT pathway for inhibition and prevention of cancer.

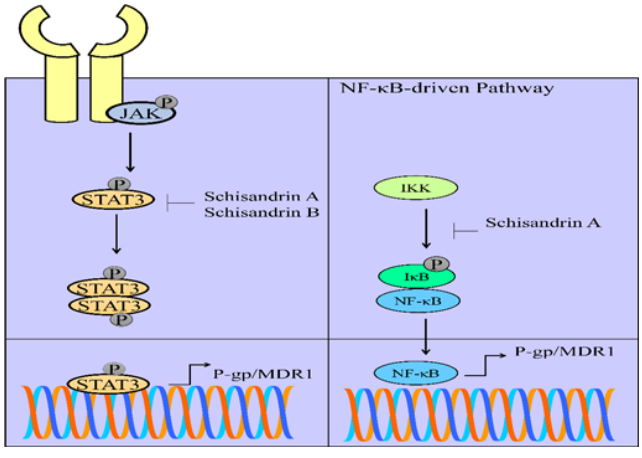

Figure 1. Schisandrin-mediated inhibition of JAK/STAT signaling and NF-κB pathway.

Apoptosis

Interest in the field of apoptosis grew rapidly with the understanding that it is a highly controlled molecular mechanism. Pioneering research works clearly indicate that apoptosis is a tightly regulated multi-step pathway primarily responsible for cell death. As we have made tremendous advancements in our understanding about the survival and death of the tumor cells in the past three decades, there is a substantial progress in the design and development of anticancer drugs.

Schisandrin B enhanced doxorubicin-induced apoptosis in DOX-resistant cancer cells (19). Doxorubicin and Schisandrin B-mediated apoptosis was impaired in survivin overexpressing- MCF-7/ADR cells. Schisandrin B promoted proteasomal degradation of survivin in DOX-resistant breast cancer cells (19).

TRAIL-based therapeutics have captured extraordinary attention because of noteworthy ability of TRAIL to induce apoptotic death in cancer cells while leaving normal cells intact. TRAIL transduced the signals through death receptors to induce apoptosis (20-25). Seminal research works have reported significant downregulation of death receptors in TRAIL-resistant cancer cells. Therefore, different natural products have been shown to stimulate cell surface expression of death receptors.

Gomisin N induced upregulation of DR4 and DR5 in HeLa cells (26). Gomisin N enhanced TRAIL-induced apoptotic death in HeLa cells. Gomisin N enhanced DR4 and DR5 via ROS production. It was shown that use of ROS scavenger markedly reduced Gomisin N-mediated upregulation of DR4 and DR5 (26).

Schisandrin B induced an increase in the levels of Bax and cleaved caspase-9. Whereas, levels of Bcl-2 were noted to be suppressed in glioma U87 and U251 cells. Intraperitoneal injections of Schisandrin B inhibited the growth of subcutaneous tumor xenografts (27). Schisandrin B also remarkably enhanced Bax, cytochrome C, caspase-9 and caspase-3 in A549 cells (28).

Schisandrin B was also found to activate intrinsic apoptotic pathway in cholangiocarcinoma cells (29). Importantly, intraperitoneal injections of Schisandrin B also effectively restricted the growth of subcutaneous HCCC-9810 tumor xenografts (29).

These findings are scientifically significant and warrant further rationally designed preclinical and clinical research. As, schisandrin has been reported to activate both extrinsic and intrinsic routes of apoptosis, therefore, it will be equally exciting to combine schisandrin with TRAIL-based therapeutics for a superior efficacy in TRAIL-resistant cancer cell lines and xenografted mice.

Regulation of protein networks by Schisandrin

Schisandrin A treatment increased the expression of Bax and p53, while significantly reduced the expression of the anti-apoptotic protein, Bcl-2 (30). Schisandrin A caused significant increase in the phosphorylation of eIF2α and also enhanced the expression of CHOP and ATF4. Schisandrin A not only reduced the expression of β-catenin but also inhibited the phosphorylated levels of GSK3β. Schisandrin A induced shrinkage of the tumors

in mice transplanted with MDA-MB-231 cancer cells. Schisandrin A significantly suppressed the expression of β-catenin and the phosphorylation of GSK3β. Levels of ATF4, Bax and p-eIF2α were increased in the tumor tissues derived from MDA-MB-231 cancer cells (30).

Schisandrin B and docetaxel combinatorially reduced N-cadherin and vimentin and increased the levels of E-cadherin (31). Schisandrin B and docetaxel markedly reduced MMP-9, NOTCH1 and β-catenin in Caski cells. Schisandrin B and docetaxel remarkably restricted tumor growth in mice transplanted with Caski cells (31).

Levels of p-FAK (Tyr 397) were noted to be reduced in colon of mice treated with dextran sulfate sodium (DSS), but schisandrin B restored phosphorylated levels of FAK in epithelial cells (32). Schisandrin B-treated colitis mice expressed higher levels of p-FAK and colon damage was less severe. Surprisingly, Schisandrin B failed to protect colon from DSS-mediated damaging and toxic effects upon inactivation of FAK which clearly highlighted that activation of FAK was crucial for protective effects of Schisandrin B. DSS-induced ulcerative colitis has main role in the initiation and progression of colitis-associated-cancer. Schisandrin B potently inhibited initiation and promotion of colitis-associated-cancer and suppressed the production of inflammatory cytokines (32).

Schisandrin B reduced the levels of cyclin D1 and CDK4 in gallbladder cancer GBC-SD and NOZ cells (33). Schisandrin B induced the levels of Bax and simultaneously reduced the levels of Bcl-2 in GBC-SD and NOZ cells. Schisandrin also inhibited the activation of NF-κB and repressed NF-κB-mediated gene network (33).

CDK4 and CDK6 phosphorylate RB protein. CDK activity is tightly regulated by CDK inhibitors (p27). Hypo-phosphorylated RB directly binds to and blocks the activity of E2F activators (E2F1-E2F3). Schisandrin C reduced the levels of CDK4 and the transcriptional factors, E2F1 and E2F4. Schisandrin C enhanced p21 (CDK inhibitor) (34).

Schisandrin A blocked the transcription of HSF1 target genes (HSP27, HSP90 and HSP70). Schisandrin A directly binds to HSF1 and prevents the activation of HSF1 (35).

Schisandrin B suppressed the levels of p-AKT, p-mTOR and MMP-9 in glioma U251 and U78 cells (36). mTOR activation led to an increase in the MMP9 expression. However, Schisandrin B inhibited mTOR-mediated increase in MMP9 expression (36).

Schisandrin B upregulated E-cadherin and downregulated vimentin and N-cadherin in H661-CSCs and NCI-H460-CSCs (Li, 37). Schisandrin B efficiently suppressed CD133, CD44, OCT4 and Bmi-1 in cancer stem cells. Schisandrin B significantly repressed the phosphorylated levels of p38MAPK. Schisandrin B inhibited tumor growth in mice subcutaneously inoculated with NCI-H460-CSCs. Schisandrin B significantly suppressed the levels of CD133, CD44, OCT4 and Bmi-1 in the tumor tissues. Moreover, Schisandrin B significantly reduced p-IκBα, p-p65 and p-p38MAPK in the tumor tissues of xenografted mice (37).

Schisandrin A enhanced the efficacy of gefitinib mainly through blockade of IKKβ activation and IKKβ-mediated inactivation of IκBα (38). Schisandrin A inhibited nuclear translocation of NF-κB. Schisandrin A exerted its IKKβ inhibitory effects by forming interactions with hydrophobic amino acids within IKKβ (38).

Regulation of non-coding RNAs by Schisandrin

Discovery and characterization of non-coding RNAs have revealed the diversity of their regulatory roles in carcinogenesis and metastasis. microRNAs (miRNAs) (39-41), long non-coding RNAs (lncRNAs) (42-45) and circular RNAs have occupied the central stage in recent years because of their indispensable role in carcinogenesis and metastasis.

Oncogenic miRNAs

Schisandrin A dose-dependently reduced the viability of MDA-MB-231 cancer cells (46). Schisandrin A significantly suppressed proliferation and inhibited migration and invasion of breast cancer cells. Schisandrin A reduced miR-155. However, treatment with miR-155 mimics counteracted the inhibitory effects exerted by Schisandrin A on the proliferation and migration of breast MDA-MB-231 cancer cells. Schisandrin A reduced the levels of p-PI3K and p-AKT but miR-155 mimics induced an increase in the levels of p-PI3K and p-AKT. Likewise, the levels of MMP2 and MMP9 were also reported to be enhanced in miR-155 mimics-transfected cancer cells (46).

Schisandrin A effectively downregulated miR-429 in thyroid cancer TPC-1 cells (fig. 2) (47). Schisandrin A inhibited cell proliferation of thyroid cancer cells by suppressing the levels of p-MEK and p-ERK in thyroid cancer cells. Likewise, Schisandrin A inhibited metastasizing potential of thyroid cancer cells by suppression of MMP2, MMP9 and vimentin (47).

Tumor suppressive miRNAs

Schisandrin A enhanced the chemosensitivity of colon carcinoma cells to 5-fluorouracil through upregulation of miR-195 (48). Schisandrin A caused marked reduction in the levels of p-PI3K and p-AKT. However, Schisandrin A did not reduce the levels of p-PI3K and p-AKT in miR-195-silenced cancer cells (48). Overall, these findings suggested that Schisandrin A-mediated upregulation of miR-195 was necessary to exert chemopreventive effects.

Schisandrin B induced an increase in the expression of miR-125a and simultaneously reduced HOTAIR in glioma U251 and U87 cells (fig.2) (49). Levels of p-mTOR were found to be enhanced in HOTAIR-overexpressing glioma cells. Migratory and invasive potential of HOTAIR-silenced glioma cells was noted to be reduced. Schisandrin B and rapamycin (mTOR inhibitor) caused significant reduction in the proliferation and migration of glioma cells (49).

CircRNAs have been shown to sponge target miRNAs and potentiate the expression of the genes. Schisandrin B induced upregulation of miR-708-5p and concordantly reduced circ_0009112 in osteosarcoma cells (50). circ_0009112 acted as an oncogenic circular RNA and fueled proliferation and migration of osteo-

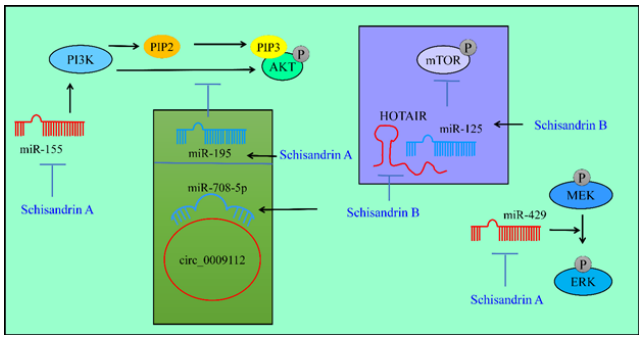

Figure 2. Regulation of non-coding RNAs by schisandrin. Different miRNAs regulate PI3K/AKT pathway in a positive and negative manner. miR-155 potentiated PI3K/AKT pathway but miR-195 and miR-708-5p inhibited the activation of PI3K/AKT pathway. miR-125 inhibited the activation of mTOR but HOTAIR promoted the activation of mTOR. Schisandrin has been shown to inhibit oncogenic miRNAs, lncRNAs and circRNAs. miR-429 potentiated MEK/ERK pathway. Schisandrin inhibited miR-429.

sarcoma cells (fig.2). p-PI3K and p-AKT levels were noted to be enhanced in circ_0009112-overexpressing osteosarcoma cells (50).

Nonetheless, these conceptual advancements represent only a smaller fraction of the snapshot of their gene regulatory properties. Importantly, integrated knowledge of schisandrin-mediated chemopreventive effects will hopefully increase the identification of functional non-coding RNAs which can be exploited pharmacologically to inhibit/prevent cancer.

How non-coding RNAs influence carcinogenesis are questions of great interest and excitement. Our evolving understanding clearly suggests that non-coding RNAs fine-tune cell specification and disease. Therefore, these functions require clear understanding, not only to provide a broader landscape of molecular mechanisms but also because non-coding RNAs can be pharmaceutically targeted with high degree of specificity.

Anti-metastatic effects of Schisandrin

Excitingly, exponential growth in the landmark discoveries related to underlying mechanisms of metastasis has unveiled a massive network of proteins involved in the multi-step regulation of the metastatic cascades.

Although pro-metastatic genes have been demonstrated to work at multiple steps in dynamically challenging process of metastasis, many of them have recently been reported to enhance the colonization step of metastasis, the process by which small clusters of tumor cells living in secondary organ sites (micro-metastasis) grow and temporally develop into lethal macro-metastasis (Fig. 3).

4T1 syngeneic xenograft models are used to analyze the intricate process of spontaneous metastasis. Therefore, major metastatic site is lung in these models. Using this model researchers reported that Schisandrin B significantly reduced 4T1 lung metastasis but did not inhibit the growth of the primary tumors (51). Schisandrin B also significantly reduced metastatic spread and homing of 4T1 cancer cells to the bone.

TGFβ induced an increase in the expression of NOX4 (NAPDH oxidase 4) (52). NOX4 was essential for generation of ROS triggered by TGFβ. TGFβ did

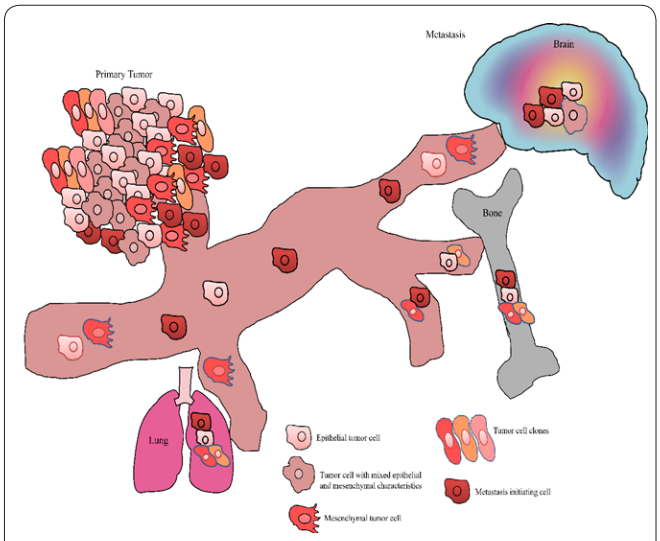

Figure 3. Distant colonization of cancer cells.

not enhance the migratory potential of NOX4-silenced 4T1 cancer cells. NOX4 knockdown caused significant suppression of the phosphorylated levels of ERK1/2 and AKT. Schisandrin B inhibited NOX4 activity. Pulmonary metastatic nodules, lung metastasis index and the rates of bone osteolysis were reported to be notably reduced in mice inoculated with NOX4-silenced 4T1 cancer cells (52).

Combinatorial use of Schisandrin with therapeutic agents

Apatinib (rivoceranib) is a small molecule that selectively targets VEGFR2. Schisandrin B and apatinib effectively induced apoptosis in gastric cancer cells (53). Schisandrin B and apatinib reduced the levels of MMP9 in gastric cancer cells. Moreover, Schisandrin B improved the efficacy of apatinib by increasing the levels of caspase-9 and Bax in gastric cancer cells (53).

Schisandrin B has been reported to be an efficient cardioprotective product apart from its scientifically acclaimed ability to inhibit multidrug resistance associated protein-1 and P-glycoprotein (54). Schisandrin B prevented doxorubicin-mediated cardiotoxicity by increasing the glutathione redox cycling (55).

Schisandrin B significantly not only reduced doxorubicin-induced toxic effects on cardiomyocytic structure but also improved cardiac functions. Schisandrin B and doxorubicin caused significant reduction in the formation of spontaneous metastatic foci in the lungs of tumor-bearing mice (56).

Schisandrin B did not increase doxorubicin-mediated apoptosis in primary human fibroblasts and primary rat cardiomyocytes (57). Schisandrin B has been shown to exert protective effects when used in combination with doxorubicin. Therefore, Schisandrin B might be a promising agent in clinical chemotherapy because of its remarkable ability to reduce the cumulative doses of doxorubicin and its associated cardiotoxicities (57).

Future prospects

Natural product research has been revolutionized by high-throughput technologies and rapidly accumulating experimental evidence has unveiled mechanistic

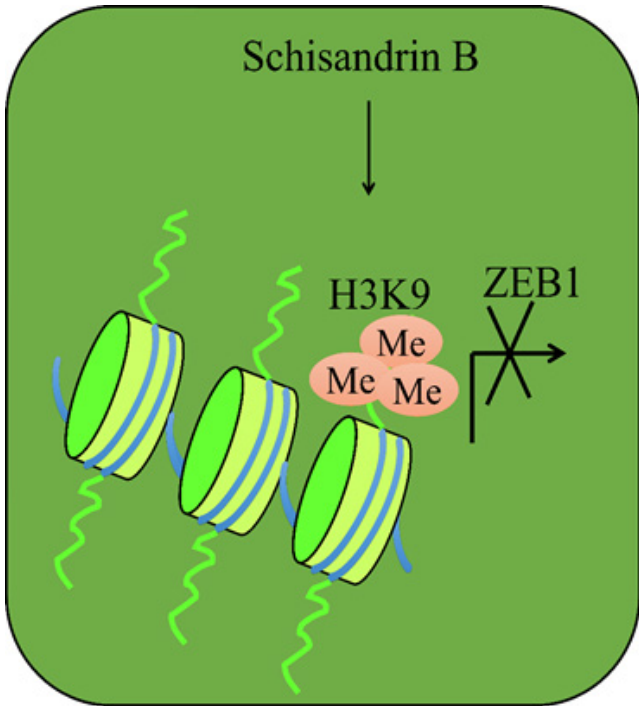

Figure 4. Epigenetic inactivation of ZEB1. Transcriptional inactivation of ZEB1 by increasing the enrichment of H3K9me3 at the ZEB1 promoter is an effective strategy to inhibit metastasis-associated genes.

analysis of pharmacological properties of myriad of high-quality bioactive components (58-61). Schisandrin has been reported to be effective in the treatment of different diseases. In this review we have exclusively focused on schisandrin mediated cancer chemopreventive effects via regulation of cell signaling pathways. We have sketched a landscape of regulation of JAK/STAT, NF-κB and non-coding RNAs by schisandrin. Schisandrin-mediated anti-metastatic effects have also been summarized and excitingly, cardioprotective effects of schisandrin are worth mentioning. This is amazingly a distinguishing and hallmark feature of schisandrin when used with chemotherapeutic drugs.

Furthermore, schisandrin mediated epigenetic regulation of genes is also an exciting area of research. Schisandrin B repressed the expression of transcriptional factor (ZEB1) in EMT by increasing the enrichment of H3K9me3 at the ZEB1 promoter and caused epigenetic inactivation (shown in fig. 4) (62).

However, there is a need to set spotlight on different signaling pathways which have not yet been explored.

Nanotechnological approaches for the delivery of Schisandrin

A major advantage of nanostructures is their multifaceted properties. The maneuverability of nanomaterial design has allowed researchers to exploit different nano-bio interactions and improve the delivery of cargo to the target sites. Accordingly, multifunctional facets of nanomaterials are of particular importance for the treatment of heterogeneous diseases. Particularly, the efficacy of anticancer nanostructures is severely limited by difficulties in the targeting, multiple biological barriers and dynamic in-vivo changes of the materials. Overall, these intricate and interconnected stumbling blocks require multi-layered countermeasures that can be achieved through multifunctionality (63-67).

Cell-penetrating-peptides (CPPs) are short peptide sequences having significant ability to penetrate the membranes (68). R8 peptide (R-R-R-R-R-R-R-R) is a promising and effective cell-penetrating-peptide. R8 modified vinorelbine and schisandrin B liposomes synergistically prolonged the median survival time of tumor-bearing mice (68).

PFVYLI (PFV) is a six amino acid cell penetrating peptide. PFV modified schisandrin B and epirubicin liposomes were found to be effective breast cancer cells. PFV modified liposomes effectively reduced the levels of VEGF, MMP9 and vimentin in breast cancer MDA-MB-435S cells (69). PFV modified schisandrin B and doxorubicin liposomes were also reported to be effective against non-small cell lung cancer cells (70).

Novel microemulsion systems co-loaded with docetaxel and schisandrin A were found to be effective against esophageal carcinoma cells (71). Intragastric administration of microemulsion system co-loaded with docetaxel and schisandrin A strikingly suppressed the tumor growth in mice inoculated with esophageal EC109 carcinoma cells. Tumor inhibition rates of microemulsion system were even higher than some of the intravenously administered nanomedicines. Mice administered with microemulsion system did not show any lesion in the liver and spleen (71).

Doxorubicin and schisandrin A were co-encapsulated into Distearoyl phosphatidylethanolamine-polyethylene glycol liposome (72). Accordingly, this long-circulating codelivery system was found to be effective against MCF-7 and HepG2. These liposomes significantly prolonged the half-life of the doxorubicin and schisandrin A, increased their circulation time, improved its bioavailability and reduced their side effects (72).

Clinical trials

Supplementation with *Schisandra chinensis* extracts enhanced skeletal muscle strength in older adults who performed low-intensity exercise (73).

Schisandra *chinensis* extracts have also been tested for efficacy in subjects with knee osteoarthritis (NCT01472822). Baofeikang granules were clinically analyzed for the treatment of combined pulmonary fibrosis and emphysema (NCT02805699). Baofeikang granules consisted of many natural products like Schisandra, saponins, Cordyceps fungi powder etc.

20-herb formulation has been clinically evaluated for efficacy in patients with Irritable bowel syndrome (NCT00676975).

Concluding remarks

Discovery of biologically active chemicals of extraordinary clinical value from medicinal plants is indeed very exciting. Mechanistic characterization of natural products for the identification of the pharmacological properties enables the researchers to decide whether or not the analysis of the target products can be extended to the advanced stages. Importantly, their structural diversities make them a valuable source of novel lead compounds against newly identified pharmacological targets in different cancers. Excitingly, tides

for the natural product research are rising and hence it can be optimistically presumed that there is a re-emergence of the era of natural product discovery through cross-fertilization of molecular biology and chemistry.

Use of simple and easily manipulated drug-like scaffolds that can mimic the functions of a complex natural product is a rapidly evolving and attractive dimension in chemical biology and drug discovery.

Therefore, integration of these exciting discoveries into a common framework will reshape the future design of effective clinical trials in this field.

Author Contributions

XL, RA, IM and IMY prepared the manuscript. AA, GB, and AAF critically edited the draft. AAF and IM designed the diagrams. GB supervised the technical aspects of the diagrams. XL, RA and AAF critically evaluated the manuscript for scientific quality. AAF ensured the lowest possible percentage of similarity index of the manuscript.

Acknowledgements

We are also grateful for the support by the International Collabrative Project of the MOST of China (#2017YFE95000). The work is also supported by the Taishan Talents project of Shandong province and the Department of Sci and Tech in Shandong Province of China (No#: ZR20MH421, # ZR20MH420 and ZR-20MH360).

References

1. Seplyarskiy VB, Sunyaev S. The origin of human mutation in light of genomic data. Nat Rev Genet. 2021 Jun 23. doi: 10.1038/s41576-021-00376-2.

2. Halasz M, Kholodenko BN, Kolch W, Santra T. Integrating network reconstruction with mechanistic modeling to predict cancer therapies. Sci Signal. 2016;9(455):ra114.

3. Jones S, Anagnostou V, Lytle K, Parpart-Li S, Nesselbush M, Riley DR, Shukla M, Chesnick B, Kadan M, Papp E, Galens KG, Murphy D, Zhang T, Kann L, Sausen M, Angiuoli SV, Diaz LA Jr, Velculescu VE. Personalized genomic analyses for cancer mutation discovery and interpretation. Sci Transl Med. 2015;7(283):283ra53. doi: 10.1126/scitranslmed.aaa7161.

4. Chen X, Wang Y, Ma N, Tian J, Shao Y, Zhu B, Wong YK, Liang Z, Zou C, Wang J. Target identification of natural medicine with chemical proteomics approach: probe synthesis, target fishing and protein identification. Signal Transduct Target Ther. 2020;5(1):72.

5. Rodrigues T, Reker D, Schneider P, Schneider G. Counting on natural products for drug design. Nat Chem. 2016;8(6):531-41.

6. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov. 2015;14(2):111-29.

7. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov. 2005;4(3):206-20.

8. Li JW, Vederas JC. Drug discovery and natural products: end of an era or an endless frontier? Science. 2009;325(5937):161-5.

9. Nasser MI, Zhu S, Chen C, Zhao M, Huang H, Zhu P. A Comprehensive Review on Schisandrin B and Its Biological Properties. Oxid Med Cell Longev. 2020 14;2020:2172740. doi: 10.1155/2020/2172740.

10.Yoganathan S, Alagaratnam A, Acharekar N, Kong J. Ellagic Acid and Schisandrins: Natural Biaryl Polyphenols with Therapeutic Potential to Overcome Multidrug Resistance in Cancer. Cells. 2021 Feb 21;10(2):458. doi: 10.3390/cells10020458.

11.Leong PK, Ko KM. Schisandrin B: A Double-Edged Sword in Nonalcoholic Fatty Liver Disease. Oxid Med Cell Longev. 2016;2016:6171658. doi: 10.1155/2016/6171658.

12.Lam PY, Ko KM. Schisandrin B as a hormetic agent for preventing age-related neurodegenerative diseases. Oxid Med Cell Longev. 2012;2012:250825. doi: 10.1155/2012/250825.

13.Thomas SJ, Snowden JA, Zeidler MP, Danson SJ. The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. Br J Cancer. 2015;113(3):365-71. doi: 10.1038/bjc.2015.233.

14.Recio C, Guerra B, Guerra-Rodríguez M, Aranda-Tavío H, Martín-Rodríguez P, de Mirecki-Garrido M, Brito-Casillas Y, García-Castellano JM, Estévez-Braun A, Fernández-Pérez L. Signal transducer and activator of transcription (STAT)-5: an opportunity for drug development in oncohematology. Oncogene. 2019;38(24):4657-4668. doi: 10.1038/s41388-019-0752-3.

15.Miklossy G, Hilliard TS, Turkson J. Therapeutic modulators of STAT signalling for human diseases. Nat Rev Drug Discov. 2013;12(8):611-29. doi: 10.1038/nrd4088.

16.Dai X, Yin C, Guo G, Zhang Y, Zhao C, Qian J, Wang O, Zhang X, Liang G. Schisandrin B exhibits potent anticancer activity in triple negative breast cancer by inhibiting STAT3. Toxicol Appl Pharmacol. 2018 ;358:110-119. doi: 10.1016/j.taap.2018.09.005.

17.Zhang ZL, Jiang QC, Wang SR. Schisandrin A reverses doxorubicin-resistant human breast cancer cell line by the inhibition of P65 and Stat3 phosphorylation. Breast Cancer. 2018;25(2):233-242. doi: 10.1007/s12282-017-0821-9.

18.Nasser MI, Han T, Adlat S, Tian Y, Jiang N. Inhibitory effects of Schisandrin B on human prostate cancer cells. Oncol Rep. 2019 Jan;41(1):677-685. doi: 10.3892/or.2018.6791.

19.Wang S, Wang A, Shao M, Lin L, Li P, Wang Y. Schisandrin B reverses doxorubicin resistance through inhibiting P-glycoprotein and promoting proteasome-mediated degradation of survivin. Sci Rep. 2017 ;7(1):8419. doi: 10.1038/s41598-017-08817-x.

20.Pitti RM, Marsters SA, Ruppert S, Donahue CJ, Moore A, Ashkenazi A. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. J Biol Chem. 1996 ;271(22):12687-90.

21.Walczak H, Miller RE, Ariail K, Gliniak B, Griffith TS, Kubin M, Chin W, Jones J, Woodward A, Le T, Smith C, Smolak P, Goodwin RG, Rauch CT, Schuh JC, Lynch DH. Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. Nat Med. 1999;5(2):157-63.

22.Pan G, O'Rourke K, Chinnaiyan AM, Gentz R, Ebner R, Ni J, Dixit VM. The receptor for the cytotoxic ligand TRAIL. Science. 1997;276(5309):111-3.

23.Zhang XD, Franco A, Myers K, Gray C, Nguyen T, Hersey P. Relation of TNF-related apoptosis-inducing ligand (TRAIL) receptor and FLICE-inhibitory protein expression to TRAIL-induced apoptosis of melanoma. Cancer Res. 1999 ;59(11):2747-53.

24.Gliniak B, Le T. Tumor necrosis factor-related apoptosis-inducing ligand's antitumor activity in vivo is enhanced by the chemotherapeutic agent CPT-11. Cancer Res. 1999 ;59(24):6153-8.

25.Roth W, Isenmann S, Naumann U, Kügler S, Bähr M, Dichgans J, Ashkenazi A, Weller M. Locoregional Apo2L/TRAIL eradicates intracranial human malignant glioma xenografts in athymic mice in the absence of neurotoxicity. Biochem Biophys Res Commun. 1999 ;265(2):479-83.

26.Inoue H, Waiwut P, Saiki I, Shimada Y, Sakurai H. Gomisin N enhances TRAIL-induced apoptosis via reactive oxygen species-mediated up-regulation of death receptors 4 and 5. Int J Oncol. 2012;40(4):1058-65. doi: 10.3892/ijo.2011.1299.

27.Li Q, Lu XH, Wang CD, Cai L, Lu JL, Wu JS, Zhuge QC, Zheng

WM, Su ZP. Antiproliferative and apoptosis-inducing activity of schisandrin B against human glioma cells. Cancer Cell Int. 2015 ;15(1):12. doi: 10.1186/s12935-015-0160-x.
28.Lv XJ, Zhao LJ, Hao YQ, Su ZZ, Li JY, Du YW, Zhang J. Schisandrin B inhibits the proliferation of human lung adenocarcinoma A549 cells by inducing cycle arrest and apoptosis. Int J Clin Exp Med. 2015 ;8(5):6926-36.
29.Yang X, Wang S, Mu Y, Zheng Y. Schisandrin B inhibits cell proliferation and induces apoptosis in human cholangiocarcinoma cells. Oncol Rep. 2016;36(4):1799-806. doi: 10.3892/or.2016.4992.
30.Xu X, Rajamanicham V, Xu S, Liu Z, Yan T, Liang G, Guo G, Zhou H, Wang Y. Schisandrin A inhibits triple negative breast cancer cells by regulating Wnt/ER stress signaling pathway. Biomed Pharmacother. 2019;115:108922. doi: 10.1016/j.biopha.2019.108922.
31.Yan C, Gao L, Qiu X, Deng C. Schisandrin B synergizes docetaxel-induced restriction of growth and invasion of cervical cancer cells in vitro and in vivo. Ann Transl Med. 2020;8(18):1157. doi: 10.21037/atm-20-6109.
32.Li J, Lu Y, Wang D, Quan F, Chen X, Sun R, Zhao S, Yang Z, Tao W, Ding D, Gao X, Cao Q, Zhao D, Qi R, Chen C, He L, Hu K, Chen Z, Yang Y, Luo Y. Schisandrin B prevents ulcerative colitis and colitis-associated-cancer by activating focal adhesion kinase and influence on gut microbiota in an in vivo and in vitro model. Eur J Pharmacol. 2019 ;854:9-21. doi: 10.1016/j.ejphar.2019.03.059.
33.Xiang SS, Wang XA, Li HF, Shu YJ, Bao RF, Zhang F, Cao Y, Ye YY, Weng H, Wu WG, Mu JS, Wu XS, Li ML, Hu YP, Jiang L, Tan ZJ, Lu W, Liu F, Liu YB. Schisandrin B induces apoptosis and cell cycle arrest of gallbladder cancer cells. Molecules. 2014 ;19(9):13235-50. doi: 10.3390/molecules190913235.
34.Park C, Choi YW, Hyun SK, Kwon HJ, Hwang HJ, Kim GY, Choi BT, Kim BW, Choi IW, Moon SK, Kim WJ, Choi YH. Induction of G1 arrest and apoptosis by schisandrin C isolated from Schizandra chinensis Baill in human leukemia U937 cells. Int J Mol Med. 2009;24(4):495-502. doi: 10.3892/ijmm_00000258.
35.Chen BC, Tu SL, Zheng BA, Dong QJ, Wan ZA, Dai QQ. Schizandrin A exhibits potent anticancer activity in colorectal cancer cells by inhibiting heat shock factor 1. Biosci Rep. 2020 ;40(3):BSR20200203. doi: 10.1042/BSR20200203.
36.Jiang Y, Zhang Q, Bao J, Du C, Wang J, Tong Q, Liu C. Schisandrin B suppresses glioma cell metastasis mediated by inhibition of mTOR/MMP-9 signal pathway. Biomed Pharmacother. 2015;74:77-82. doi: 10.1016/j.biopha.2015.07.006.
37.Li S, Wang H, Ma R, Wang L. Schisandrin B inhibits epithelial-mesenchymal transition and stemness of large-cell lung cancer cells and tumorigenesis in xenografts via inhibiting the NF-κB and p38 MAPK signaling pathways. Oncol Rep. 2021;45(6):115. doi: 10.3892/or.2021.8066.
38.Xian H, Feng W, Zhang J. Schizandrin A enhances the efficacy of gefitinib by suppressing IKKβ/NF-κB signaling in non-small cell lung cancer. Eur J Pharmacol. 2019 ;855:10-19. doi: 10.1016/j.ejphar.2019.04.016.
39.Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006 ;103(7):2257-61.
40.Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. Proc Natl Acad Sci U S A. 2007 ;104(23):9667-72.
41.Khraiwesh B, Arif MA, Seumel GI, Ossowski S, Weigel D, Reski R, Frank W. Transcriptional control of gene expression by microRNAs. Cell. 2010 ;140(1):111-22.
42.Cabili MN, Dunagin MC, McClanahan PD, Biaesch A, Padovan-Merhar O, Regev A, Rinn JL, Raj A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. Genome Biol. 2015 ;16(1):20. doi: 10.1186/s13059-015-0586-4.
43.Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015;47(3):199-208.
44.Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL, Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458(7235):223-7.
45.Chiu HS, Somvanshi S, Patel E, Chen TW, Singh VP, Zorman B, Patil SL, Pan Y, Chatterjee SS; Cancer Genome Atlas Research Network, Sood AK, Gunaratne PH, Sumazin P. Pan-Cancer Analysis of lncRNA Regulation Supports Their Targeting of Cancer Genes in Each Tumor Context. Cell Rep. 2018 Apr 3;23(1):297-312.e12.
46.Yan H, Guo M. Schizandrin A inhibits cellular phenotypes of breast cancer cells by repressing miR-155. IUBMB Life. 2020 Aug;72(8):1640-1648. doi: 10.1002/iub.2329.
47.Ding Q, Li X, Sun Y, Zhang X. Schizandrin A inhibits proliferation, migration and invasion of thyroid cancer cell line TPC-1 by down regulation of microRNA-429. Cancer Biomark. 2019;24(4):497-508.
48.Kong D, Zhang D, Chu X, Wang J. Schizandrin A enhances chemosensitivity of colon carcinoma cells to 5-fluorouracil through upregulation of miR-195. Biomed Pharmacother. 2018;99:176-183. doi: 10.1016/j.biopha.2018.01.035.
49.Jiang Y, Zhang Q, Bao J, Du C, Wang J, Tong Q, Liu C. Schisandrin B inhibits the proliferation and invasion of glioma cells by regulating the HOTAIR-micoRNA-125a-mTOR pathway. Neuroreport. 2017 ;28(2):93-100. doi: 10.1097/WNR.0000000000000717.
50.Wang B, Wang X, Tong X, Zhang Y. Schisandrin B Inhibits Cell Viability and Migration, and Induces Cell Apoptosis by circ_0009112/miR-708-5p Axis Through PI3K/AKT Pathway in Osteosarcoma. Front Genet. 2020 ;11:588670. doi: 10.3389/fgene.2020.588670.
51.Liu Z, Zhang B, Liu K, Ding Z, Hu X. Schisandrin B attenuates cancer invasion and metastasis via inhibiting epithelial-mesenchymal transition. PLoS One. 2012;7(7):e40480. doi: 10.1371/journal.pone.0040480.
52.Zhang B, Liu Z, Hu X. Inhibiting cancer metastasis via targeting NAPDH oxidase 4. Biochem Pharmacol. 2013 ;86(2):253-66. doi: 10.1016/j.bcp.2013.05.011.
53.Li YJ, Liu HT, Xue CJ, Xing XQ, Dong ST, Wang LS, Ding CY, Meng L, Dong ZJ. The synergistic anti-tumor effect of schisandrin B and apatinib. J Asian Nat Prod Res. 2020;22(9):839-849. doi: 10.1080/10286020.2019.1645131.
54.Sun M, Xu X, Lu Q, Pan Q, Hu X. Schisandrin B: a dual inhibitor of P-glycoprotein and multidrug resistance-associated protein 1. Cancer Lett. 2007 ;246(1-2):300-7. doi: 10.1016/j.canlet.2006.03.009.
55.Li L, Pan Q, Han W, Liu Z, Li L, Hu X. Schisandrin B prevents doxorubicin-induced cardiotoxicity via enhancing glutathione redox cycling. Clin Cancer Res. 2007 ;13(22 Pt 1):6753-60. doi: 10.1158/1078-0432.CCR-07-1579.
56.Xu Y, Liu Z, Sun J, Pan Q, Sun F, Yan Z, Hu X. Schisandrin B prevents doxorubicin-induced chronic cardiotoxicity and enhances its anticancer activity in vivo. PLoS One. 2011;6(12):e28335. doi: 10.1371/journal.pone.0028335. Epub 2011. Erratum in: PLoS One. 2012;7(1).doi:10.1371/annotation/7a1b01e4-b894-40ef-9c31-

584e9c24ee0a.
57.Li L, Lu Q, Shen Y, Hu X. Schisandrin B enhances doxorubicin-induced apoptosis of cancer cells but not normal cells. Biochem Pharmacol. 2006 ;71(5):584-95. doi: 10.1016/j.bcp.2005.11.026.
58.Sivasankarapillai VS, Madhu Kumar Nair R, Rahdar A, Bungau S, Zaha DC, Aleya L, Tit DM. Overview of the anticancer activity of withaferin A, an active constituent of the Indian ginseng Withania somnifera. Environ Sci Pollut Res Int. 2020;27(21):26025-26035. doi: 10.1007/s11356-020-09028-0.
59.Behl T, Sharma A, Sharma L, Sehgal A, Singh S, Sharma N, Zengin G, Bungau S, Toma MM, Gitea D, Babes EE, Judea Pusta CT, Bumbu AG. Current Perspective on the Natural Compounds and Drug Delivery Techniques in Glioblastoma Multiforme. Cancers. 2021; 13(11):2765. https://doi.org/10.3390/cancers13112765
60.Behl T, Sharma A, Sharma L, Sehgal A, Zengin G, Brata R, Fratila O, Bungau S. Exploring the Multifaceted Therapeutic Potential of Withaferin A and Its Derivatives. Biomedicines. 2020 ;8(12):571. doi: 10.3390/biomedicines8120571.
61.Kaur I, Behl T, Sachdeva M, Bungau S, Venkatachalam T. Exploring the Mitochondrial Apoptotic Cell Death Landscape and Associated Components Serving as Molecular targets, primarily for synthetic and natural drugs targeting oncology therapeutics. Curr Mol Pharmacol. 2021 Jan 20. doi: 10.2174/1874467214666210120145537.
62.Zhuang W, Li Z, Dong X, Zhao N, Liu Y, Wang C, Chen J. Schisandrin B inhibits TGF-β1-induced epithelial-mesenchymal transition in human A549 cells through epigenetic silencing of ZEB1. Exp Lung Res. 2019;45(5-6):157-166. doi: 10.1080/01902148.2019.1631906.
63.Schroeder A, Heller DA, Winslow MM, Dahlman JE, Pratt GW, Langer R, Jacks T, Anderson DG. Treating metastatic cancer with nanotechnology. Nat Rev Cancer. 2011;12(1):39-50. doi: 10.1038/nrc3180.
64.Williams RM, Chen S, Langenbacher RE, Galassi TV, Harvey JD, Jena PV, Budhathoki-Uprety J, Luo M, Heller DA. Harnessing nanotechnology to expand the toolbox of chemical biology. Nat Chem Biol. 2021;17(2):129-137. doi: 10.1038/s41589-020-00690-6.
65.Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5(3):161-71. doi: 10.1038/nrc1566.
66.Goldberg MS. Improving cancer immunotherapy through nanotechnology. Nat Rev Cancer. 2019;19(10):587-602. doi: 10.1038/s41568-019-0186-9.
67.Wang J, Li Y, Nie G. Multifunctional biomolecule nanostructures for cancer therapy. Nat Rev Mater. 2021 :1-18. doi: 10.1038/s41578-021-00315-x.
68.Li XY, Shi LX, Yao XM, Jing M, Li QQ, Wang YL, Li QS. Functional vinorelbine plus schisandrin B liposomes destroying tumor metastasis in treatment of gastric cancer. Drug Dev Ind Pharm. 2021;47(1):100-112. doi: 10.1080/03639045.2020.1862169.
69.Jing M, Bi XJ, Yao XM, Cai F, Liu JJ, Fu M, Kong L, Liu XZ, Zhang L, He SY, Jia LQ, Li XT. Enhanced antitumor efficacy using epirubicin and schisandrin B co-delivery liposomes modified with PFV via inhibiting tumor metastasis. Drug Dev Ind Pharm. 2020;46(4):621-634. doi: 10.1080/03639045.2020.1742145.
70.Cai FY, Yao XM, Jing M, Kong L, Liu JJ, Fu M, Liu XZ, Zhang L, He SY, Li XT, Ju RJ. Enhanced antitumour efficacy of functionalized doxorubicin plus schisandrin B co-delivery liposomes via inhibiting epithelial-mesenchymal transition. J Liposome Res. 2021;31(2):113-129. doi: 10.1080/08982104.2020.1745831.
71.Su X, Gao C, Shi F, Feng X, Liu L, Qu D, Wang C. A microemulsion co-loaded with Schizandrin A-docetaxel enhances esophageal carcinoma treatment through overcoming multidrug resistance. Drug Deliv. 2017;24(1):10-19. doi: 10.1080/10717544.2016.1225854.
72.Xu SY, Su H, Zhu XY, Li XY, Li J, Chen X, Wang Q, Hao RY, Yan XY. Long-circulating Doxorubicin and Schizandrin A Liposome with Drug-resistant Liver Cancer Activity: Preparation, Characterization, and Pharmacokinetic. J Liposome Res. 2021 :1-50. doi: 10.1080/08982104.2021.1884093.
73.Cho YH, Lee SY, Lee CH, Park JH, So YS. Effect of Schisandra chinensis Baillon extracts and regular low-intensity exercise on muscle strength and mass in older adults: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2021 Jun 1;113(6):1440-1446. doi: 10.1093/ajcn/nqaa447.