Phytomedicine Plus 2 (2022) 100202

Contents lists available at ScienceDirect

Phytomedicine Plus

journal homepage: www.sciencedirect.com/journal/phytomedicine-plus

Therapeutic and pharmacological potential of Tanshinones against lung cancer: A systematic review

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ARTICLE INFO

Keywords:
Tanshinones
Tanshinone I
Tanshinone IIA
Cryptotanshinone
Lung cancer
Systematic review

ABSTRACT

Background: Lung cancer is the most prevalent of all cancers, causing the highest number of cancer-related deaths in men and the second-highest number in women worldwide. Recent advancements in cancer treatment have witnessed a paradigm shift of therapeutic approaches towards natural products. Several *in vitro* and *in vivo* studies have revealed the effective therapeutic potential of Tanshinones against various forms of cancer, including lung carcinomas. Therefore, a systematic assessment of the potential therapeutic efficacy of Tanshinones against lung cancer will provide important insights for their possible clinical application.
Purpose: This review was designed to study the therapeutic and pharmacological potential of Tanshinones against lung cancer in a systematic manner.
Methods: This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements. An extensive systematic search for literature on Tanshinones against lung cancer was performed in PubMed and Google Scholar databases using specific keywords. All the relevant articles published between January 2010 and April 2021 were considered.
Results: Out of the total 9,170 articles screened, 29 articles were selected for the present study based on the eligibility criteria. Among the included articles, 19 studies were conducted *in vitro* on lung cancer cell lines, 2 studies were performed *in vivo* on mice models, and 8 studies were conducted both *in vitro* and *in vivo*. The findings of the studies indicate that Tanshinones exhibit therapeutic potential against lung cancer by triggering various cellular processes such as oxidative stress, apoptosis, and cell cycle arrest and decreased mitochondrial potential, leading to cancer cell death or diminishing cell proliferation.
Conclusion: The systematic review suggests the promising therapeutic potential of Tanshinones against lung carcinogenesis. However, the studies conducted so far were on lung cancer cell lines and mice models only. Therefore, to validate the translational potential of Tanshinones in clinical settings, more studies including human clinical trials with a large sample size are warranted.

Introduction

Currently, cancer is the second most lethal disease with increasing cancer-related mortality. Lung cancer is the most common form of cancer with an estimated 2.2 million newly diagnosed cases causing 1.8 million deaths in 2020 worldwide (Sung et al., 2021). It is the primary cause of cancer-related morbidity and mortality in men. In women, it is the third cause of morbidity after breast and colorectal cancer and the second cause of mortality after breast cancer. Small cell lung cancer

; MTT, 3-(4,5-Dimethylthiazol-2-yl)−2,5-Diphenyltetrazolium Bromide; NSCLC, Non-small cell lung cancer; PARP, Poly (ADP-ribose) polymerase.

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https://doi.org/10.1016/j.phyplu.2021.100202
Received 20 September 2021; Received in revised form 9 December 2021; Accepted 14 December 2021
Available online 17 December 2021

Abbreviations

ATF6	Activating transcription factor-6
CDK	Cyclin-dependent kinase
CHOP	C/EBP-homologous protein
CSCs	Cancer Stem Cells
DR	Death receptor
EGF	Epidermal growth factor
ER	Endoplasmic reticulum
IRE1	Inositol - requiring enzyme-1
MAPK	Mitogen-activated protein kinase
g cancer;	PARPPoly (ADP-ribose) polymerase
PERK	Protein kinase RNA- like endoplasmic reticulum kinase
PPAT	phosphoribosyl pyrophosphate aminotransferase
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
ROS	Reactive oxygen species
SCLC	Small cell lung cancer
STAT3	Signal transducer and activator of transcription 3
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
VEGF	Vascular endothelial growth factor;

(SCLC) and non-small cell lung cancer (NSCLC) are the two wide categories of lung cancer (Zhang et al., 2018). NSCLC accounts for approximately 85–88% of all lung cancer cases and, SCLC accounts for 12–15% (Tung et al., 2013). Conventional cancer therapies are associated with several adverse side effects such as intolerance, drug resistance, and toxic effects on healthy cells. Therefore, plant-derived natural products are considered as safe treatment alternatives for their potent therapeutic efficacies and lower side effects.

Salvia miltiorrhiza is a well-documented herb in Traditional Chinese Medicine that belongs to the Lamiaceae family. The dried root of this herb, known as Danshen, has long been used as a therapy against cardiovascular and cerebrovascular diseases (Jiang et al., 2019). Tanshinones, a class of lipophilic bioactive components are commonly found in the roots of *S. miltiorrhiza*. The most important bioactive compounds of Tanshinones are Tanshinone I, Tanshinone IIA, cryptotanshinone, and dihydrotanshinone. Accumulating evidence suggests that Tanshinones display significant therapeutic potential against various types of cancer such as liver, prostate, breast, colorectal, and lung cancer (Ansari et al., 2021; Chen et al., 2013; Gao et al., 2020; Jiang et al., 2019). Recent *in vitro* as well as *in vivo* studies have revealed the possible mechanisms by which Tanshinones exhibit anticancer activity that prominently comprise the inhibition of tumor growth and proliferation, metastasis, invasion, and angiogenesis, and induction of oxidative stress, apoptosis, autophagy, and cell cycle arrest (Chen et al., 2014).

A systematic assessment of the therapeutic efficacy and pharmacology of Tanshinones is essential before considering further experimental as well as clinical studies against lung carcinogenesis. Therefore, this review envisages studying the therapeutic potential and pharmacological effects of Tanshinones on lung cancer cells and their underlying mechanisms in a systematic fashion. Further, the various signaling pathways in lung cancer perturbed by the Tanshinones have also been highlighted. This study will further our understanding of the therapeutic applications of Tanshinones against lung cancer.

Methods

Search strategy

This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. To identify suitable articles for this review, extensive searches were conducted on Google Scholar and PubMed databases. Only those articles published between January 2010 and April 2021 were considered for this study. Following keywords were used for the literature search:

(i) “Tanshinone IIA" and "lung cancer”.
(ii) “Tanshinone I" and "lung cancer”.
(iii) “Cryptotanshinone" and "lung cancer” and
(iv) “Dihydrotanshinone" and "lung cancer”.

Eligibility criteria and study selection

The search results were carefully assessed and only the studies fulfilling the eligibility criteria were selected for this study. After evaluating through all the eligibility criteria, potentially relevant studies were considered for full-text assessment and finally, the articles that met the following eligibility criteria were considered for the present systematic review.

Articles fulfilling the following inclusion criteria were selected: (i) Articles with “Tanshinone IIA/Tanshinone I/cryptotanshinone or dihydrotanshinone and lung cancer” in the titles, (ii) Articles written in English language, (iii) Articles which were revealed in peer review journals, and (iv) Original research articles.

Similarly, certain articles were removed based on the following exclusion criteria: (i) Articles written in a language other than English and (ii) Articles that don’t have “Tanshinone IIA/Tanshinone I/cryptotanshinone or dihydrotanshinone and lung cancer” in the titles.

Results and discussion

Features of included articles

Out of a total of 9,170 articles screened, 29 articles were finally selected after fulfilling the inclusion criteria. Out of these 29 articles, 19 studies were based on lung cancer cell lines, 2 studies were based on mice models and 8 studies were conducted both *in vitro* as well as *in vivo*. **Fig. 1** schematically shows the search strategy and selection of the relevant studies performed according to the guidelines of PRISMA statement. All the included studies reported the anticancer properties of Tanshinones against lung cancer. There were a total of 3 studies on Tanshinone I, 12 studies on Tanshinone IIA, 11 studies on cryptotanshinone and, 3 studies on total Tanshinones. However, no report could be found on dihydrotanshinone against lung cancer. The natural source and structures of the Tanshinones that show anticancer activity against lung cancer are depicted in **Fig. 2**.

Anti-Cancer efficacy of Tanshinones on lung cancer

The *in vitro* studies on lung cancer cell lines, as well as the *in vivo* studies on xenograft mice models of lung cancer have revealed the effective therapeutic potential of Tanshinones. They have been reported to exert tumoricidal effects by perturbing various cellular mechanisms such as induction of endoplasmic reticulum (ER) stress, cell cycle arrest, apoptosis and autophagy, inhibition of cell proliferation, migration, invasion and angiogenesis, and enhancing antitumor immunity. An outline of the included studies depicting molecular pharmacology and potential therapeutic intervention by Tanshinones on lung cancer is presented in **Table 1**. Tanshinones have been reported to inhibit cancer growth and proliferation by targeting oncogenes and transcription factors as well as modulating miRNA expression. Treatment with Tanshinones has been found to effectively sensitize the otherwise resistant lung cancer cells towards a standard therapy regimen (Kim et al., 2016; Wang et al., 2019a; Xia et al., 2015; Yan et al., 2018). In addition, they also enhance the therapeutic efficiency of other chemotherapeutic drugs such as cisplatin and adriamycin, thereby showing synergistic effects in

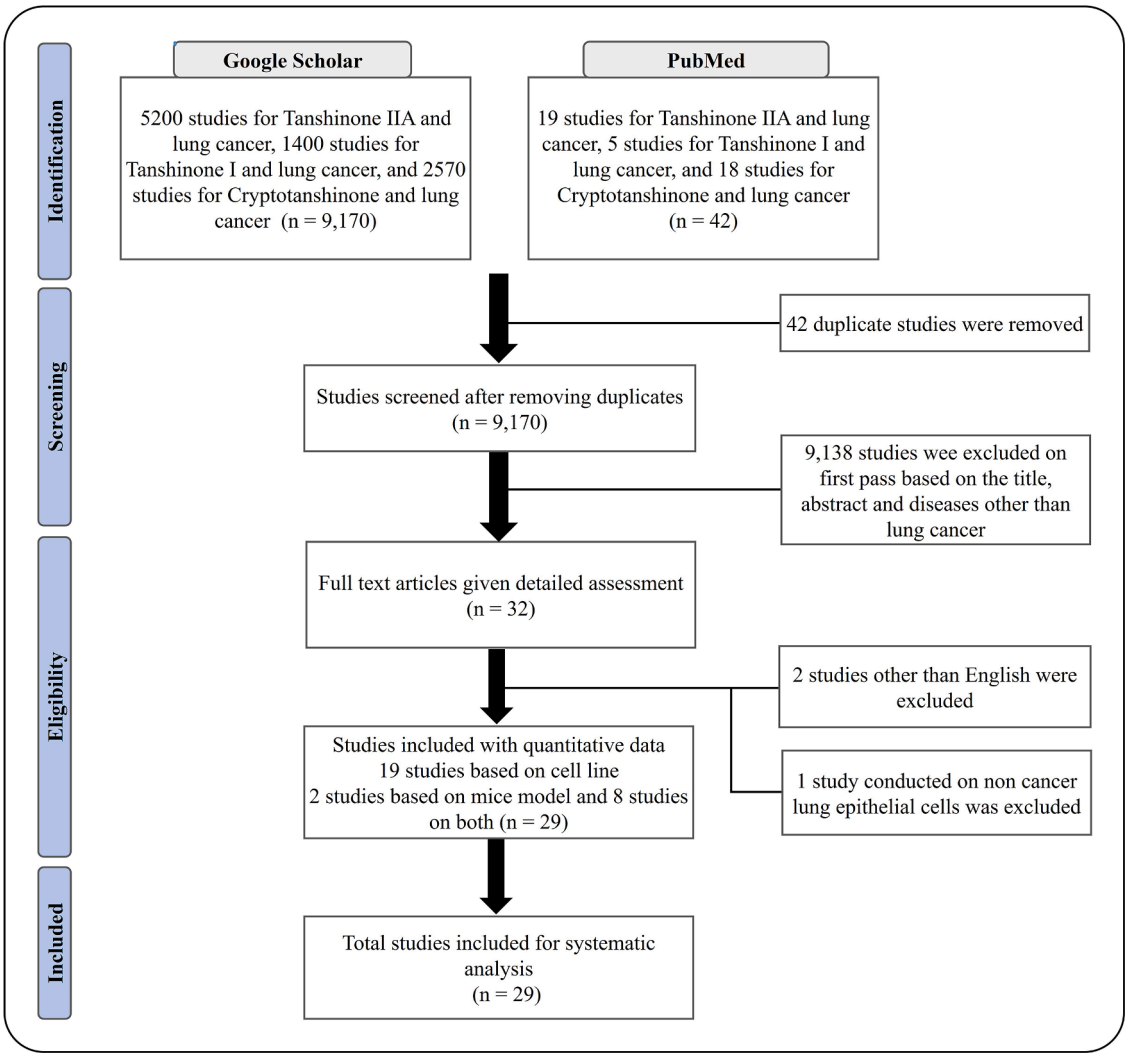

Fig. 1. Schematic representation of the search strategy used for the retrieval of relevant literature and selection of the studies as per PRISMA guidelines.

the treatment of lung cancer (Liao et al., 2019; Xie et al., 2016). The mechanisms and pharmacological effects by which Tanshinones exhibit anticancer activity as identified in this systematic review are depicted in **Fig. 3** and are discussed in the following sections.

Inhibition of cancer cell proliferation

Uncontrolled and abnormal cell proliferation in the lungs leads to the development of lung cancer that may invade neighboring tissue during metastasis. Suppression of lung cancer cell growth and proliferation by Tanshinones is one of the main parameters studied in all the included articles. Notably, Li et al. (2013) showed that all the Tanshinones: Tanshinone I, Tanshinone IIA and cryptotanshinone inhibited the cell proliferation in lung cancer in a dose-dependent manner . Moreover, Tanshinones were also found to effectively inhibit the colony formation of H1299 cells. Zhang and co-workers found that cryptotanshinone could effectively inhibit the proliferation of lung cancer A549 cells in a concentration-dependent manner as confirmed by MTT based cell viability assay (Zhang et al., 2018). Moreover, treatment with cryptotanshinone also remarkably prevented the colony formation of A549 cells in a concentration-dependent manner (Zhang et al., 2018). By the assay of clonogenicity, the cytotoxic effects of cryptotanshinone have been demonstrated on A549 cells by inhibiting cancer cell proliferation (Chen et al., 2014). Cryptotanshinone may forbid cell survival via suppression of the IGF-1R/PI3K/Akt pathway in A549 cells (Zhang et al., 2018). Moreover, Tanshinone IIA was also found to effectively inhibit the growth of gefitinib-resistant lung cancer cell lines (Takeuchi et al., 2014). Various modes of inhibition of cancer cell proliferation by Tanshinones are discussed in the subsequent sections.

Cell cycle arrest

Abnormal progression of the cell cycle leads to the transformation of a normal cell into cancer cell, therefore arresting the cell cycle has been envisioned as a promising approach for the prevention of cancer growth and proliferation. The cell cycle is regulated by several protein kinase complexes consisting of cyclin and cyclin-dependent kinase (Cdk). Tanshinones have been reported to display anti-proliferative activity against malignant cells by modulating various cell cycle regulatory proteins, which culminates in the cell cycle arrest (**Fig. 3**). Tanshinone I suppressed the expression of cyclin A and cyclin B to down-regulate the progression of the cell cycle through S and G2/M phases (Tung et al., 2013). In another study, it has been found that Tanshinone I and cryptotanshinone arrested cell cycle at S phase and tanshinone IIA at G2/M phase by down-regulating cyclin A, cyclin B, aurora A, p-cdc and, CDK2 proteins (Li et al., 2013). Cryptotanshinone has been reported to increase the expression of p53 and suppress both Cdc2 and cyclin B1, resulting in halting of the cell cycle at the G2/M phase in Lewis lung carcinoma cells (Liu et al., 2019). In addition, cryptotanshinone down-regulated the expression of cell cycle regulatory proteins of G1

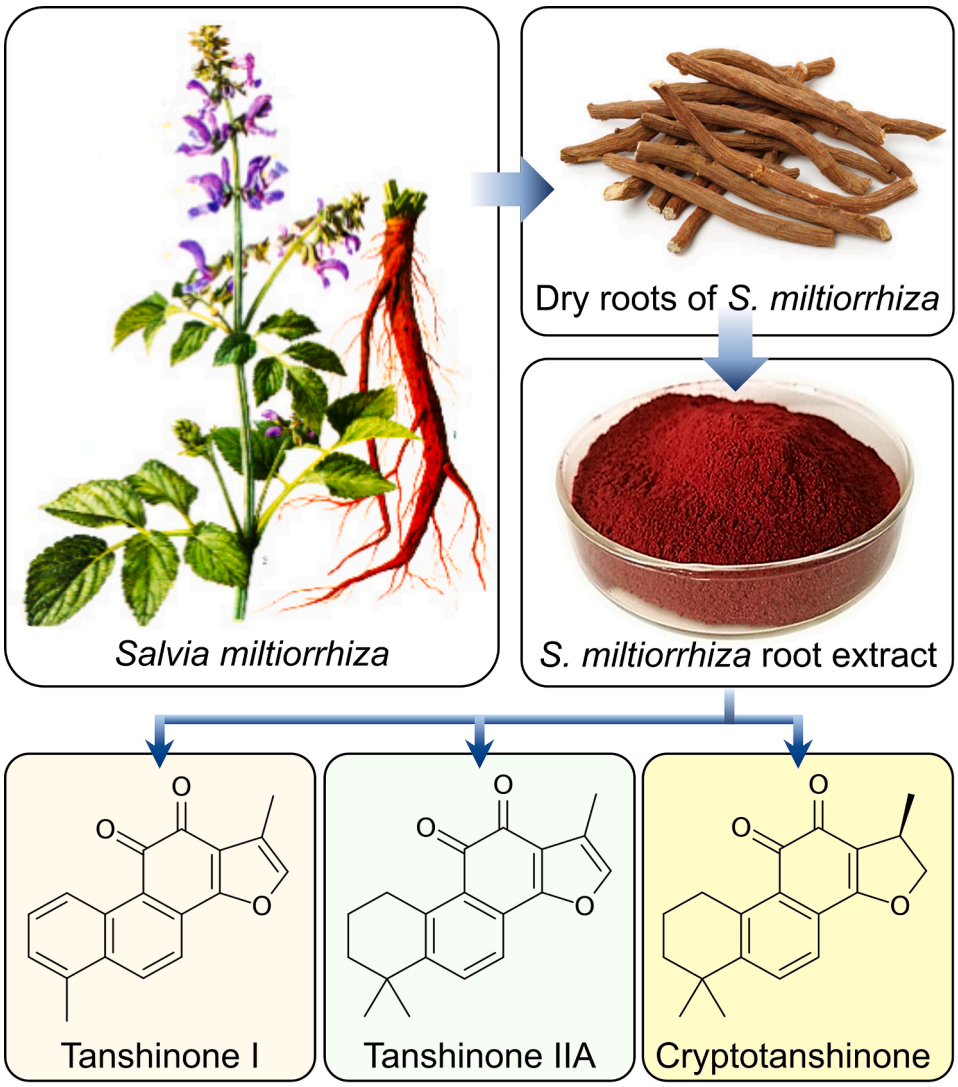

Fig. 2. Source and structures of Tanshinones with therapeutic potential against lung cancer.

phase (cyclin D, E, Cdk4) and S phase (cyclin A, Cdk 2), and was found to trigger cell cycle arrest in A549 and H460 cells, respectively (Kim et al., 2018). In a study, the cryptotanshinone was reported to mediate the induction of G2/M phase arrest via down-regulating the expression of cyclin B1, CDK1, and Cdc25C (Chen et al., 2014). Thus, the various checkpoints of the cell cycle offer ideal therapeutic targets for Tanshinones in lung cancer.

Induction of ER stress

ER is an important organelle that is involved in the synthesis of lipids, maintenance of the calcium reserves, and the acquisition of the native 3D configuration of newly synthesized proteins which are subsequently translocated to their target sites. Improper functioning of ER can lead to the accumulation of misfolded proteins within them, thus causing ER stress (Adams et al., 2019). During homeostasis, ER stress triggers the unfolded protein response machinery comprising protein kinase RNA-like endoplasmic reticulum kinase (PERK), activating transcription factor-6 (ATF6), and inositol-requiring enzyme-1 (IRE1) to mitigate the effects of unfolded proteins, and aids in the survival of the cell. However, excessive ER stress leading to the prolonged activity of the PERK pathway has been found to induce programmed cell death by up regulating the expression of death receptors (DR) and other pro-apoptotic factors. Tanshinone IIA was reported to induce ER stress pathway in NSCLCs by increasing the expression of death receptor 5 (DR5) and C/EBP-homologous protein (CHOP) via activation of PERK/ATF4 signaling that aid to induce apoptosis (Kim et al., 2016). Moreover, Tanshinone IIA treatment of NSCLCs was also found to impair the signal transducer and activator of transcription 3 (STAT3) signaling pathway and downregulate the expression of anti-apoptotic protein survivin. Furthermore, the cumulative effects of Tanshinone IIA sensitized the NSCLCs to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)mediated apoptosis in resistant cancer cells. Although, a role of reactive oxygen species (ROS) has been speculated in activating Tanshinone IIA mediated ER stress response in A549 cells, a detailed analysis of the underlying mechanism is warranted to further explore the therapeutic potential of Tanshinones in cancer treatment. In another study, ROS has been demonstrated to initiate programmed cell death as well as protective autophagy in cancer cells (Gao et al., 2015).

Induction of apoptosis

The loss of apoptosis facilitates tumor initiation, progression, and cancer cell survival. Therefore induction of apoptosis in tumor cells serves as an ideal goal for cancer therapeutic intervention. Tanshinones display their potent anticancer activity by inducing apoptosis in lung

Table 1
Potential therapeutic roles and molecular pharmacology of various Tanshinones against lung cancer as reported in the included articles.

Sl No	Tanshinones	Cell line/model	Mechanism of action	Molecular pharmacology / Targeted signaling pathways	References
1	Tanshinone I	H1299 human lung cancer cells; H1299 tumor in mouse model	Induction of apoptosis; Cell cycle arrest; Inhibition of angiogenesis	→ Supressed the expression of cyclin A, cyclin B, aurora A, p-cdc and CDK2. → Increased Bax/Bcl-2 ratio. → Aurora A was identified as a vital target for tanshinone I.	(Li et al., 2013)
2	Tanshinone I	A549, CL1–0, and CL1–5 lung cancer cells; Transgenic mouse model	Cell cycle arrest; Inhibition of cell invasion and migration; Inhibition of angiogenesis	→ Supressed the expression of the VEGF, Cyclin A, and Cyclin B. → Suppressed the levels of activated ERK2. → Reduced the VEGF expression.	(Tung et al., 2013)
3	Tanshinone I	Lung cancer radio-resistant cell lines, H358-IR and H157-IR	Inhibition of cell proliferation and clone formation; Enhancing radiosensitivity in radioresistant lung cancer cells	→ Suppressed the expression of pro-oncogenic protein PPAT	(Yan et al., 2018)
4	Tanshinone IIA	H146 human lung cancer cells	Inhibition of cell proliferation; Induced the apoptosis	→ Increased production of ROS and Ca2+, → Decreased mitochondrial membrane potential. → Increased Bax/Bcl-2 ratio. → Raise the expression of GADD15 and caspase 3 → Supressed expression of the NF-κBp65.	(Cheng and Su, 2010)
5	Tanshinone IIA	A549 human lung cancer cells	Inhibition of cell proliferation; Induced the apoptosis	→ Increased production of ROS and Ca2+, → Decreased mitochondrial membrane potential. → Increased expression of p53 → Increased Bax/Bcl-2 ratio → Increased cytochrome-c release	(Chiu and Su, 2010)
6	Tanshinone IIA (*in vivo*)	A549 cells and H596-NQO1 cells	Induction of apoptosis	→ p53-independent and NQO1 dependent apoptosis.	(Liu et al., 2012)
7	Tanshinone IIA	NSCLC cells: gefitinib-sensitive PC-9; gefitinib-resistant PC-14, AY-01, H358, H1650, and A549	Inhibition of cancer cell growth	→ Increased production of ROS	(Takeuchi et al., 2014)
8	Tanshinone IIA	A549 human lung cancer cells	Inhibition of cell proliferation; Induction of apoptosis	→ Loss of mitochondrial membrane potential → Release of cyt c from mitochondria. → Bax levels is raised and activated caspase 9 and caspase 3. → Activation of JNK signaling	(Zhang et al., 2014)
9	Tanshinone IIA	A549 human lung cancer cells	Inhibit the cell proliferation; Cell cycle arrest; Induction of apoptosis; Inhibition of invasion and migration	→ Suppressed the VEGF/VEGFR2 pathway. → Suppressed the PI3K/AKT pathway	(Xie et al., 2015)
10	Tanshinone IIA and TRAIL	TRAIL-resistant NSCLC cells: A549, H596, H1299 and Calu-1	Synergistic inhibitory effect with TRAIL on cell proliferation; Induction of apoptosis and ER stress	→Increased the expression of caspase 3, caspase 8 and cleaved PARP. → Induced the protein level of CHOP and DR5 by activating PERK/ATF4 signal.	(Kim et al., 2016)
11	Tanshinone IIA and cyclophosphamide	Lewis lung cancer mouse model	Synergistic effect; Induction of apoptosis; Inhibition of angiogenesis; Enhanced anti-tumor immunity	→ Bax/Bcl-2 ratio was increased. → Reduced the expression of VEGF → Higher $CD4^+$ and $CD4^+/CD8^+$ T cells → Higher NK cell activity	(Li et al., 2016)
12	Tanshinone IIA and adriamycin	Human NSCLC cell lines A549 and PC9	Synergistic effect; Cell cycle arrest; Induction of apoptosis; Inhibition of cell invasion and migration	→Supressed the activity of VEGF/PI3K/Akt signaling pathway. → Reduced the expression of VEGF, VEGFR2.	(Xie et al., 2016)
13	Tanshinone IIA and cisplatin	Human NSCLC cell lines A549, PC9, H1299, and SPA-A1; Mouse xenograft model	Synergistic effect; Cell cycle arrest; Induction of apoptosis; Inhibition of cell invasion and migration	→ Inhibition of the PI3K/Akt pathway → Increased expression of Bax and cleaved Caspase-3	(Liao et al., 2019)
14	Tanshinone IIA	Gefitinib resistant NSCLC cells: HCC827 /gefitinib, Mouse xenograft model	Sensitization of gefitinib-resistant cells to gefitinib; Inhibition of cell proliferation; Induction of apoptosis	→ Downregulation of the VEGFR2/Akt pathway	(Wang et al., 2019a)
15	Tanshinone IIA	Human NSCLC cell lines HCC827, H1975, and A549; *In vivo* mouse model	Inhibition of cell proliferation; Induction of apoptosis	→ Reduced EGFR signaling by inhibiting phosphorylation. → Increased expression of caspase 3 and cleaving PARP-1. → Induced Mcl-1 degradation by down-regulating EGFR-Akt signaling	(Gao et al., 2020)
16	Cryptotanshinone	A549 human lung cancer cells; Mouse xenograft model	Growth-inhibition; Induction of apoptosis; Cell cycle arrest	→ Supressed cyclin B1, CDK1 and Cdc25C → Up-regulation of p21 → Increased level of p53 and Bax and decreased level of Bcl2	(Chen et al., 2014)
17	Cryptotanshinone				

(*continued on next page*)

Table 1 (*continued*)

Sl No	Tanshinones	Cell line/model	Mechanism of action	Molecular pharmacology / Targeted signaling pathways	References
		A549 and cisplatin resistant A549/DDP cells	Restored the sensitivity of cisplatin resistant cells towards cisplatin	→ Supressed the expression of Nrf2 → Down-regulation of MAPKs, AKT and STAT3 pathways.	(Xia et al., 2015)
18	Cryptotanshinone	Human SCLC cells H446	Inhibition of cell proliferation	→ Increased CD4+ T cell cytotoxicity via activation of JAK2/STAT4 pathway	(Man et al., 2016)
19	Cryptotanshinone	Human NSCLC cell line A549 and H460	Cell cycle arrest; Induction of apoptosis	→ Increased expression of cleaved caspase-3, cleaved caspase-9, cleaved PARP, and Bax as well as decreased the Bcl2. → Down-regulated the expression of cyclin D, E, Cdk 4, cyclin A and Cdk2. → Inhibition of PI3K/Akt/GSK-3β Pathway.	(Kim et al., 2018)
20	Cryptotanshinone	A549 and H1299 human lung cancer cells	Inhibition of cell proliferation; Inhibition the migration	→ Suppressed the IGF-1R and Akt phosphorylation → Inhibition of IGF-1R/PI3K/Akt pathway	(Zhang et al., 2018)
21	Cryptotanshinone	Lewis lung carcinoma; Mouse model for lung cancer	Cell cycle arrest; Inhibit the cell proliferation; Enhanced antitumor immunity	→ Increased expression of p53 and down-regulated of both Cdc2 and cyclin B1 → Promoted maturation of DC in a MyD88 dependent manner. → Activation of NF-κB, p38, and JNK.	(Liu et al., 2019)
22	Cryptotanshinone	NSCLC cell lines: HCC827, H1299, H1975, A549 and HEK293T	Cell cycle arrest; Inhibition of cell proliferation	→ Inhibited the expression of EGFR. → Suppression of lung cancer through regulating miR-146a-5p/EGFR axis	(Qi et al., 2019)
23	Cryptotanshinone	A549 human lung cancer cells	Inhibition of cell proliferation; Inhibit the invasion and migration	→ Decreased expression of MMP14 via up-regulation of miR-133a	(Wang et al., 2019b)
24	Cryptotanshinone	NSCLC stem cells	Attenuates the stemness; Enhanced sensitivity of TKI and chemotherapy	→ Reduced expression of stemness markers oct4 and nanog → Reduced spheroid forming ability → Decreased activity of ALDH1 → Activated the Hippo pathway → Decreased the expression of TAZ and its targeted genes- CTGF, TIF-1 and Smad2.	(Jin et al., 2020)
25	Cryptotanshinone	SW900 lung cancer cell line	Induction of apoptosis	→ Increased antitumor activity in combination with standard drugs	(Vundavilli et al., 2020)
26	Cryptotanshinone	Human NSCLC cell lines: A549, H1299 and H1975. Mouse xenograft model	Increased the activity of gefitinib on NSCLC cells; Induction of apoptosis	→ Inhibition of transketolase expression via Nrf2.	(Cao et al., 2021)
27	Total Tanshinones	Human NSCLC cell line 95D	Induction of apoptosis Induction of autophagy	→ Intracellular ROS generation → Depolarized mitochondrial membrane potential → Increased Bax/Bcl-2 ratio → Increased cytochrome c and cleaving PARP-1 → Up-regulated the expression of Beclin-1, Atg3, Atg5, Atg7, and Atg12	(Gao et al., 2015)
28	Tanshinones	Human NSCLC cell line H1299	Cell cycle arrest; Induction of apoptosis	→ Suppressed AURKA via up-regulating of miR-32 expression	(Ma et al., 2015)
29	Tanshinones	NSCLC cells A549 and SPCA-1 cells	Cell cycle arrest; Inhibition of cell proliferation; Induction of apoptosis	→ Up-regulation of miR-137 expression	(Zhang et al., 2016)

cancer cells (**Fig. 3**). Tanshinone IIA was reported to induce apoptosis in lung cancer cells by increasing the production of the ROS and accumulation of Ca^{2+}, decreasing the mitochondrial membrane potential and increasing the Bax/Bcl-2 ratio (Cheng and Su, 2010; Chiu and Su, 2010; Gao et al., 2015; Liu et al., 2012). The resultant increased Bax/Bcl-2 ratio further induced release of cytochrome c from mitochondria into cytosol which causes caspase-3 activation leading to the induction of apoptosis in lung cancer cells (Cheng and Su, 2010; Chiu and Su, 2010; Gao et al., 2015; Zhang et al., 2014). In a recent study, Gao et al. (2020) reported that Tanshinone IIA increased the levels of cleaved poly (ADP-ribose) polymerase (PARP) as well as cleaved-caspase-3, thus causing apoptosis in NSCLC cells . These apoptotic effects were induced by the down-regulation of the genes along the epidermal growth factor receptor (EGFR)/ protein kinase B (Akt) signaling axis. By inhibiting the phosphorylation of EGFR and its downstream target Akt, Tanshinone IIA treatment led to the subsequent ubiquitination and destabilization of the pro-survival factor: myeloid cell leukemia 1 (Mcl-1). Also, the inhibition of EGFR signaling has been reported to prevent the sequestration of pro-apoptotic factor Bim via Mcl-1 by impairing their interaction. Consistently, the reduction in the levels of Mcl-1 by tanshinone IIA was found to induce the activation of pro-caspase 3 and a reduction in the mitochondrial membrane depolarization. Interestingly, Mcl-1 has been implicated in aggravating the resistance of NSCLCs to tyrosine kinase inhibitors harbouring EGFR activating mutations. Cryptotanshinone also induced apoptosis by enhancing the activation of caspase-3, caspase-9, and expression of cleaved PARP, pro-apoptotic protein Bax and p53 as well as decreasing the expression of anti-apoptotic protein Bcl-2 (Chen et al., 2014). In an earlier study, it was shown that all the Tanshinones induced apoptosis in lung cancer cells by significantly increasing the Bax/Bcl-2 ratio (Li et al., 2013). Overall, induction of apoptosis represents a key mechanism by which Tanshinones exhibit anticancer activity. The emerging data suggest that the treatment of cancer cells with naturally occurring compounds such as Tanshinones can serve to overcome the resistance of cancer cells to conventional drugs, and therefore can help to extend the existing pipeline of available drugs in the effective treatment of cancer.

Induction of autophagy

Autophagic cell death is an intracellular lysosome-dependent

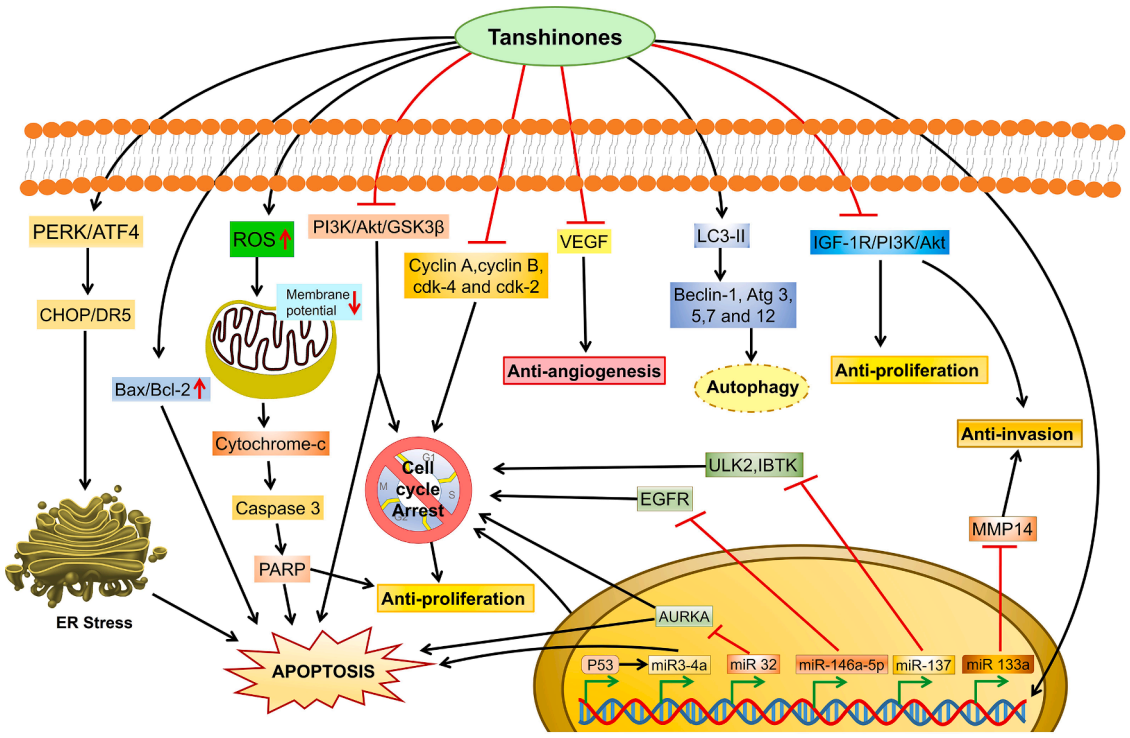

Fig. 3. Mechanisms of anticancer activity of Tanshinones and the targeted signaling pathways in lung cancer.

catabolic pathway involving the formation of the double-membrane autophagosomes in which cellular constituents are engulfed. It is a cell-protective event that regulates cellular homeostasis, and reduced autophagy has been linked to tumor development (Jung et al., 2020). Tanshinones have been reported to increase the expression of LC3-II along with other autophagic proteins such as Beclin-1, Atg3, Atg5, Atg7, and Atg12 in a concentration-dependent manner in 95D lung cancer cells (Gao et al., 2015). This study suggests that Tanshinones induce protective autophagy in lung cancer cells by increasing ROS in the cells. Regulation of autophagy in tumor cells plays a dual role in progression as well as suppression of cancer (Yun and Lee, 2018). Therefore, more evidence-based studies are required to investigate the role of Tanshinones in the induction of autophagy and treatment of lung cancer.

Inhibition of angiogenesis

Angiogenesis is the process of new capillary blood vessel formation that plays a critical role in cancer development. Prevention of this process serves as an important approach for cancer therapy. The vascular endothelial growth factor (VEGF) plays a pivotal role in angiogenesis and vascularization of tumor mass (Yoo and Kwon, 2013). Tanshinone IIA has been found to significantly down-regulate the expression of VEGF and VEGF receptor 2 (VEGFR2) in human NSCLC A549 cells suggesting its possible role in angiogenesis inhibition (Xie et al., 2015). Moreover, Tanshinone IIA was found to remarkably lower the VEGF expression and increase the expression of Angiostatin and Endostatin in the Lewis mice lung cancer model suggesting the inhibition of angiogenesis in the tumor tissue (Li et al., 2016). This anti-angiogenic effect was found to be more potent when the cancer cells were co-treated with cyclophosphamide. Moreover, the Tanshinone I was also reported to suppress angiogenesis in lung cancer by down-regulating VEGF (Li et al., 2013; Tung et al., 2013).

Inhibition of tumor invasion

Tumor invasion and migration involve a complex pathway that leads the cancer cells to invade the nearby tissue which helps to spread cancer throughout the body. Targeting the aspects associated with metastasis offers an effective approach for cancer therapy. It has been reported that cryptotanshinone treatment significantly inhibited the migration of A549 cells in a concentration-dependent manner (Zhang et al., 2018). Moreover, the treatment of gefitinib-resistant NSCLC cells, HCC827/gefitinib with a combination of Tanshinone IIA and gefitinib not only sensitized the cells towards gefitinib but also prevented their migration (Wang et al., 2019a). The combined effects of gefitinib and Tanshinone IIA suppressed the level of p-EGFR in HCC827/gefitinib cells, by targeting the VEGFR2/Akt pathway. Nevertheless, further investigations are required to validate the anti-metastatic effect of all the tanshinones before considering them as a therapeutic agent against metastatic lung cancer.

Targeting oncogenes and transcription factors

Tanshinones have been reported to suppress the expression of the AURKA gene that codes for aurora A, a member of serine/threonine kinases that help in maturation of centrosome, formation of the spindle, and G2/M progression. The overexpression of AURKA has been reported in many cancer types, and its reduced expression has been found to diminish tumor growth, and hence it is considered an oncogene. Tanshinones were found to prevent the proliferation of NSCLC by suppressing the expression of AURKA (Ma et al., 2015). Moreover, Tanshinone I has also been reported to suppress Aurora A expression, leading to the inhibition of cancer cell proliferation (Li et al., 2013).

Targeting miRNA expression

MicroRNAs (miRNAs) are a class of non-coding RNAs, 18–23 nucleotides long that regulate the post-transcriptional expression of target genes. The miRNAs may regulate the tumor-related genes and can serve

a potential role in lung cancer therapy (Wang et al., 2019b). As has been mentioned in the previous section that the high expression of the AURKA gene is associated with cancer and hence it serves as an important molecular target for cancer therapy. It has been reported that the expression levels of miRNAs (let-7b/c, miR-25, miR-32, miR-34a, miR-92a/b, miR-137, miR-363, and miR-367) were remarkably increased by the treatment of Tanshinones (Ma et al., 2015). This study further focussed on the anti-oncogenic effects of miR-32 in lung cancer cells. After performing luciferase reporter assay the investigators observed that miR-32 binding site was present at 3′-UTR (357–379 base pair) of AURKA. The data suggest that Tanshinones can down-regulate AURKA by up-regulating the expression of miR-32 in NSCLC cells (Ma et al., 2015). Moreover, Tanshinones could also increase the expression of miR-137 in NSCLC cells, which subsequently down-regulates positive regulators of cell cycle such as ULK2 and IBTK, thereby leading to cell cycle arrest and reducing cancer cell proliferation (Zhang et al., 2016). Cryptotanshinone has also been reported to increase the expression of miRNAs: miR-30d-5p, miR-126-3p, miR-133a, miR-338-3p, and miR-451a in A549 cells. Among these miRNAs, miR-133a expression was significantly increased and was found to reduce the expression of matrix metalloproteinase-14 (MMP14), and thus preventing the metastasis of A549 cells (Wang et al., 2019b). Furthermore, cryptotanshinone induced expression of miR-146a-5p has been reported to reduce the expression of EGFR resulting in reduced cell proliferation via the miR-146a-5p/EGFR axis (Qi et al., 2019).

Sensitizing therapy-resistant tumors

The development of therapy resistance during cancer treatment acts as a major challenge to the conventional therapeutic regime. Therefore, sensitizing the resistant cells towards the same or different standard therapy is crucial for successful cancer management (Leary et al., 2018). Tanshinones have been reported to sensitize various therapy-resistant lung cancer cells. Treatment with Tanshinone IIA sensitized the TRAIL resistant NSCLC cells A549, H596, H1299, and Calu-1 and increased the TRAIL-induced cell death (Kim et al., 2016). In a recent study, it has been showed that Tanshinone IIA reversed the gefitinib-resistant NSCLC cells HCC827 /gefitinib *in vitro* as well as *in vivo* mouse xenograft model via inhibition of VEGFR/Akt pathway (Wang et al., 2019a). Tanshinone I was also found to inhibit the proliferation and colony formation of radio-resistant H358-IR and H157-IR lung cancer cells and enhance the radio-sensitivity by down-regulating the expression of pro-oncogenic protein phosphoribosyl pyrophosphate aminotransferase (PPAT) (Yan et al., 2018). Cryptotanshinone has also been found to sensitize the chemo-resistant lung cancer A549/DDP cells towards cisplatin by down-regulating Nrf2 and Nrf2 target genes, rendering them susceptible towards cisplatin treatment, leading to cell death by apoptosis (Xia et al., 2015). Moreover, cryptotanshinone also sensitizes the resistant cancer cells by targeting several pathways such as MAPKs, Akt, and STAT3 involved in the development of chemoresistance.

Enhancing anti-tumor immunity

Strengthening the immunity against tumors is one of the most effective and safe therapeutic approaches for various types of cancer. Several studies have implicated Tanshinones in boosting anti-tumor immunity against lung cancers. Cryptotanshinone was found to inhibit the proliferation of human SCLC cells H446 by inducing cytotoxicity in regulating $CD4^+$ T cells via activation of the JAK2/STAT4 pathway suggesting an interesting role of cryptotanshinone in cancer immunotherapy (Man et al., 2016). The immunotherapeutic potential of cryptotanshinone was also reported to induce the maturation of human as well as mouse dendritic cells (DCs) in a MyD88-dependent manner (Liu et al., 2019). DC maturation was accompanied by the up-regulation of co-stimulatory and MHC molecules and the production of TNFα, IL-1β, and IL-12p70. The cryptotanshinone-induced maturation of DC also involved NF-κB, p38, and JNK activation. Previous studies also reported significantly higher levels of $CD4^+$ T cells, $CD4^+/CD8^+$ratio, and NK cell activity in Lewis mice with lung cancer after treatment with Tanshinone IIA in combination with cyclophosphamide (Li et al., 2016). These studies indicate that Tanshinones can effectively enhance the anti-tumor immunological activity suggestive of their therapeutic potential in cancer immunotherapy.

Synergistic effects

Several studies have reported that the Tanshinones enhance the antitumor activity of other known anticancer drugs. Tanshinone IIA and cisplatin both exhibit an anti-proliferative effect on NSCLC cells in a concentration-dependent manner. Interestingly, the combination of Tanshinone IIA and cisplatin showed a significantly higher anti-proliferative effect than their individual administration (Liao et al., 2019). The combination of Tanshinone IIA and cisplatin synergistically prevented the proliferation of NSCLC cells A549, PC9, H1299, and SPA-A1 by inhibiting metastasis, inducing cell cycle arrest and apoptosis. Co-treatment of Tanshinone IIA and cisplatin also synergistically prevented xenograft tumor cell proliferation via suppression of the PI3K/Akt signaling pathway (Liao et al., 2019). Moreover, the combination of Tanshinone IIA and adriamycin synergistically reduced the viability of lung cancer A549 and PC9 cells by down-regulating the VEGF/PI3K/Akt signaling as well as increasing the expression of Bax, cleaved caspase-3 and suppressing the expression of VEGF, VEGFR2, Bcl-2 and Caspase-3 proteins (Xie et al., 2016). A combination of Tanshinone IIA and TRAIL synergistically reduced cell viability and induced apoptosis in TRAIL-resistant NSCLC cells by up-regulating DR5 and down-regulating survivin via selective activation of PERK/ATF4 and inhibition of STAT3, respectively (Kim et al., 2016). Another combination of Tanshinone IIA with gefitinib was also reported to synergistically inhibit the proliferation of gefitinib-resistant NSCLC cells (Wang et al., 2019a). Therefore, Tanshinone IIA can be considered as a novel agent for combination therapy for the treatment of lung cancer. Likewise, cryptotanshinone augmented the effect of gefitinib on NSCLC cells by inhibiting the activity of transketolase, a key component of the pentose phosphate pathway (Cao et al., 2021). The overexpression of transketolase has been reported in various tumors and serves to enhance the intracellular levels of NADPH in cancer cells. The elevated levels of NADPH protect the cancer cells from ROS mediated oxidative stress and the associated cell death. However, the treatment of NSCLCs with cryptotanshinone was found to prevent the expression of transketolase by downregulating its activating transcription factor, Nrf2. As a result, the cryptotanshinone treated cancer cells were characterized by elevated levels of ROS and an overstretched G1 phase of the cell cycle, leading to their apoptosis. The finding was further validated in the murine xenograft model with grafted gefitinib-resistant H1975 and PC9/GR lung cancer cells, wherein the co-treatment with cryptotanshinone and gefitinib was found to significantly inhibit the proliferation of xenografted tumors (Cao et al., 2021). In another study, it has been showed that a combination of cryptotanshinone with other drugs significantly induced apoptosis in the SW900 lung cancer cell line (Vundavilli et al., 2020). However, more such studies on the synergistic role of Tanshinones would be required in animal and human subjects.

Tanshinones targeting cancer stem cells

Cancer stem cells (CSCs) are responsible for tumor initiation, therapy resistance, and cancer relapse. CSCs have the ability of self-renewal, differentiation, and initiate tumor growth. Therefore, targeting the CSCs represents an efficient therapeutic approach for cancer management (Uddin and Hoque, 2021). A recent study reported that cryptotanshinone reduced spheroid formation and expression of ALDH1 and stemness marker Oct4 and Nanog in NSCLC CSCs, thus attenuating the stemness of the cancer cells (Jin et al., 2020). Cryptotanshinone

activated the Hippo pathway by decreasing the nuclear level of TAZ by promoting its translocation to the cytoplasm. Additionally, they also reported that crytotanshinone enhanced the sensitivity of NSCLC CSCs to tyrosine kinase inhibitors and chemotherapy (Jin et al., 2020). However, further studies are required on the possible effects of Tanshinones on CSCs.

Conclusion

Tanshinones exhibit promising therapeutic potential against lung cancer by exerting various mechanisms. They have been shown to exhibit anticancer activity by modulating various signaling pathways leading to the induction of cell cycle arrest, apoptosis, autophagy, and prevention of angiogenesis, proliferation, invasion, and migration. However, further research is required to validate the studies with more animal models and also in human subjects. Since resistance to chemotherapeutic drugs has been a major obstacle in the treatment of cancers, further studies are required to understand the mechanism by which Tanshinones can improve the efficacy of available drugs in resistant cancer cells. Moreover, they should be largely explored for their synergistic efficacy and immunotherapeutic potential. Thus, the Tanshinones may be considered as promising drug candidates for the treatment of human lung cancer.

CRediT author statement

Syed Sahajada Mahafujul Alam: Data curation, Writing- Original draft preparation and Editing. **Faizan Uddin:** Writing- Reviewing and Editing. **Farheen Badrealam Khan:** Reviewing and Editing. **Mohammad Amjad Kamal:** Reviewing and Editing, Validation. **Mehboob Hoque:** Conceptualization, Writing- Reviewing and Editing, Supervision, Validation.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors sincerely acknowledge the Department of Biological Sciences, Aliah University, Kolkata, India for providing the necessary facilities for research. SSMA acknowledges the Council of Scientific & Industrial Research (CSIR) Govt. of India for financial assistance in the form of Junior Research Fellowship (JRF).

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