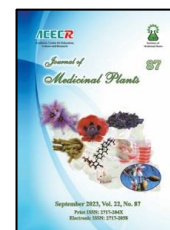




Institute of
Medicinal Plants

Journal of Medicinal Plants

Journal homepage: www.jmp.ir



Review Article

Herbal nano-formulations in lung cancer: Superiorities to original forms

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ARTICLE INFO

Keywords:

Medicinal plant
Lung cancer
Curcumin
Quercetin
Green tea
Marsdenia tenacissima

ABSTRACT

Background: LC (Lung cancer) is the most common type of cancer and has an increased mortality and morbidity rate throughout the world. Although radiation therapy, chemotherapy, and surgical approaches are among the common curative strategies against LC, these methods have not enough efficacies and may cause adverse effects. As a result, identifying alternative ways in order to treat and control LC patients is necessary. **Objective:** In this narrative review, we argued about the curative influences nano-based herbal medicine (Curcumin, Green tea, quercetin, and *Marsdenia tenacissima*) and their comparison with the focus on their mechanistic aspects against LC. **Methods:** The databases of Google Scholar, Web of Science, PubMed, Scopus, and SID were searched, with no date limitation for articles published in English. **Results:** The evaluation results showed these herbal products through various mechanisms, such as regulating the immune system, stimulating cell apoptosis, and autophagy, can be helpful in LC treatment. However, the co-use of herbal medicine and nano-formulations, namely Zinc oxide NPs (Nano particles), CdS QDs (cadmium sulfide quantum dots), NPs conjugated with AuNPs (Au nanoparticles), can dramatically overcome some limitations of herbal medicine and increase its efficacy against LC. **Conclusion:** It seems that the use of nanoformulations and herbal medicine improve LC. However, more studies with large sample sizes are needed to prove these findings.

1. Introduction

Cancer is described by uncontrolled and progressive division of the cell [1]. Among diverse types of this disease, lung cancer (LC) is the most prevalent cancer and has mounting

mortality and morbidity rate globally [2, 3]. LC is organized into two main types, small-cell lung cancer (SCLC), which is responsible for 15 % of cases, and non-small-cell lung cancer (NSCLC) that involves 85 % of LC patients [4,

Abbreviations: LC, Lung cancer; NPs, Nano particles; CdS QDs, cadmium sulfide quantum dots; AuNPs, Au nanoparticles

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doi:

Received 23 July 2023; Received in revised form 25 October 2023; Accepted 5 November 2023

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5]. It is thought that SCLC is originated from the lymphatic system agents because SCLC is microscopically similar to the cells of lymphoma [6]. SCLC, as a malignant disorder of the epithelium, comprises small cells with slight cytoplasm, unclear cell border, granular nuclear chromatin, and absent or colorless nucleoli [6]. On the contrary, NSCLC is characterized as a type of malignant epithelial tumor of the lung without a small-cell component [7]. It consists of three subgroups, including squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large cell carcinoma (LCC) [8, 9, 10]. LC can manifest some signs and symptoms such as hemoptysis, cough, chest pain, dyspnea, and hoarseness. Also LC is along with Pancoast syndrome, superior vena cava syndrome, and plural involvements [11]. The common therapeutic ways for LC, based on the stage and total status of cancerous cells, include radiation therapy, chemotherapy, and surgical methods [12]. However, the prognosis of LC patients who underwent these methods is undesirable [13]. Moreover, the present curative approaches are unsatisfactory and can lead to harmful influences [14]. For instance, cases undergoing chemotherapeutic drugs may experience some adverse effects, such as severe myelosuppression, vomiting, and nausea [15]. Therefore, finding novel and alternative treatments is crucial for patients with LC [14]. Lately, herbal therapy has been introduced as an effective therapeutic strategy against different types of cancer especially LC via improvement of life quality, survival rate, and physiological conditions [16-18]. On the other hand, nanotechnology has created a new outlook for treating various diseases like cancers. The physicochemical features of nanostructures have provided many advantages for early detection

and delivering the drugs in order to better improvement of cancer patients [19, 20]. The aim of present study is to discuss the curative influences of herbal products with a focus on some attractive highly researched herbal products, namely, Curcumin, Green tea, Quercetin, and *Marsdenia tenacissima*, as well as their nano-formulation, with a focus on their mechanistic aspects against LC.

Data collection method

For this purpose, related papers in the English language were collected up to July 2021. The keywords of Curcumin, Green tea, Quercetin, and *Marsdenia tenacissima*, lung cancer, herbal products, plant formulations, nano- based formulations, nanoherbal, were searched in Scopus, Google Scholar, and PubMed databases.

Pathogenesis of lung cancer

In the past years, our information about LC pathogenesis has been elevated. In this regard, there are numerous mechanisms that give rise to the preneoplastic respiratory epithelial cells and finally LC [21]. It is addressed that some mutations can increase cancer susceptibilities, such as retinoblastoma, p53, and epidermal growth factor receptor (EGFR) mutations. Furthermore, the reduced ability of Deoxyribonucleic acid (DNA) repair can have an important role in lung carcinogenesis [22]. It is highlighted that dysregulation of inflammatory status can stimulate oncogenesis and trigger angiogenic factors, which increase the proliferation and expansion of tumor cells (Figure 1.) [23]. Tumors have an ability to elevate the entrance of myelomonocytic cells, comprising myeloid-derived suppressor cells (MDSCs), angiopoietin-1 receptor-expressing monocytes, and macrophages that can express

inflammatory factors [24]. The inflammation is considered as an initial step of tissue to remove pathogenic agents in order to restore the physiological functions of injured tissue [25]. Dysregulated inflammation also has a role in the onset, progression, and metastasis of tumors [26]. A piece of documents showed that reactive oxygen species (ROS) related to the inflammation, reactive nitrogen species (RNS), epigenetic changes, genomic instability, impaired activation of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and epithelial-to-mesenchymal transformation (EMT) are among the probable mechanisms by which the inflammation participates in the transformation of malignant cells (Figure 1.) [27-30]. The production of reactive nitrogen species (RNS) or reactive oxygen species (ROS), which can be resulted from the inhalation of air pollutants, like nitrogen dioxide, sulfur dioxide, diesel soot, and automobile exhaust, can lead to chemokine and proinflammatory cytokine production [25]. The formation of cytokines and inflammatory factors have been in turn linked with the proliferation and metastasis of tumor cells [31]. Several transcription factors and inflammatory cytokines are involved in LC, for example, interleukin (IL)-1 β , interleukin 6, signal transducer and activator of transcription 3 (STAT3), and tumor necrosis factor α [32]. Regarding the immunopathogenesis of LC, both adaptive and innate immune agents, such as neutrophils, macrophages, B cells, and natural killer cells, have a role in both pro-tumor and anti-tumor functions. Particularly, the pro-tumor and anti-tumor aspects of T cells in cancer progression have been attracted great attention [33]. T cells have different roles in the immune reaction and are significantly associated with LC biology. It is express that CD8⁺ cytotoxic T

lymphocytes augment immunosurveillance through the recognition of T cell receptor of antigens that are bound to major histocompatibility complex-I. When these T lymphocytes are activated, they secrete granzyme B, perforin, and interferon-gamma γ that take part in the cytolysis of tumor cells [34]. In addition, CD4⁺T cell subsets, for instance, T helper 17 and T cells, have been suggested as key actors in inflammation-related disorders like cancer. These two subtypes can enhance the pro-tumor environment by the elevation and preservation of a pro-tumor and immuno-inhibitor inflammation environment which can cause tumorigenesis, metastasis, and cancer progression [35]. Forkhead box class O1 (FOXO1) is a transcription factor that is downregulated in NSCLC. FOXO1 overexpression suppresses NSCLC cell migration and tumor growth, while silenced FOXO1 boosts the migration and proliferation of these tumor cells. These findings are indicating that FOXO1 is a potent modulator of LC which can be used in LC therapy approaches [36]. NF-kappaB is another transcription factor that plays a role in LC. There is growing data that NF-kappaB is triggered in several tumor types, such as lung, pancreatic, and breast cancer. In spite of the heterogenic features of lung tumors, the appraisal of samples of LC cases revealed the increased levels of NF-kappaB activity in both NSCLC and SCLC. Furthermore, this transcription factor is related to disease progression and weak prognosis in the LC subjects [37]. Besides, it is stated that zinc finger E-box binding homeobox 1 (ZEB1) expression is related to metastasis and tumor grade in LC probably because of its function in epithelial-to-mesenchymal transformation, which is known as a late occurrence of tumorigenesis [38]. Plus, in numerous cancer

cell lines, like LC, STATs such as STAT3 and STAT5 are activated [39]. In LC, a number of signaling pathways are involved. For instance, the aberrant triggering of the Wnt/ β -catenin signaling pathway in lung cancer has a role in the onset, progression, recurrence, metastasis, and chemo-resistance [40]. Autophagy, as an essential constituent of cellular defense, has a complex role in cancer initiation, progression, and therapy. Autophagy can exert anti-cancer effects by subcellular debris clearance, mitochondrial preservation, inflammation regulation, and recycling of metabolic debris. On the contrary, the pro-survival impacts of autophagy may promote the survival of tumor cells under adverse situations and lead to cancerous cell resistance to chemotherapy. In contrast, it has been manifested that autophagy can improve the curative effects of chemotherapy drugs through autophagy-dependent cell death [41]. Also, the continuous

activation of autophagy gives rise to programmed cell death (apoptosis). Apoptosis has a striking role in eliminating transformed or mutated cells, and thus one of the landmarks of cancerous cells is evasion from apoptosis. Apoptosis is adjusted by extracellular and/or intracellular signals and changes some of the morphological properties of targeted cells, such as condensation and fragmentation of the nucleus, mitochondrial outer membrane permeabilization, cell shrinkage, membrane blebbing, and the formation of the apoptotic body [42, 43]. Some reports have confirmed that female sex hormones, especially estrogen hormones, may have a role in LC. In this line, two estrogen receptors, Estrogen receptor alpha ($ER\alpha$) and Estrogen receptor beta ($Er\beta$), have been identified in LC patients. The existence of $ER\alpha$ has been approved in the cell lines of NSCLC, whereas $Er\beta$ overexpression has a prognosticating role in this type of LC [44].

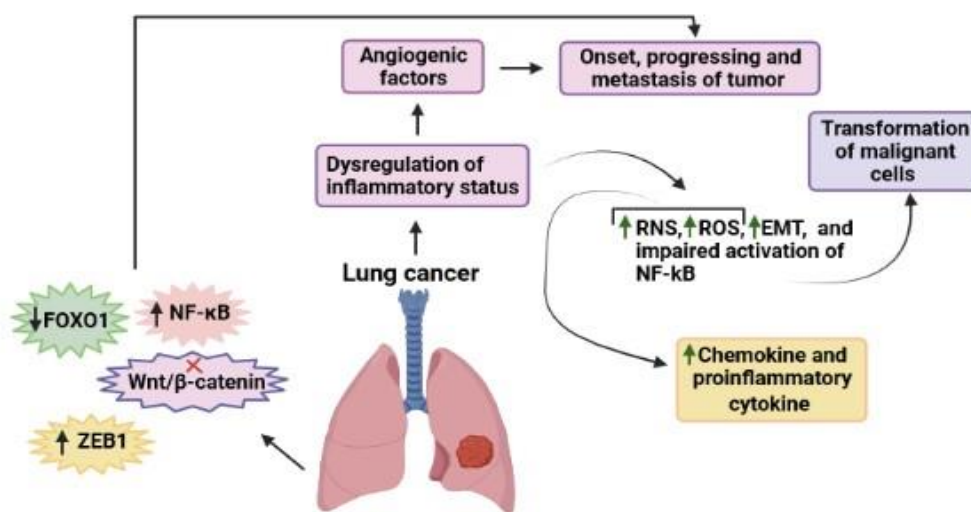


Fig. 1. Pathogenesis of lung cancer. NF- κ B, Nuclear factor-kappa B; FOXO1, Forkhead Box O1; ZEB1, Zinc Finger E-Box Binding Homeobox 1; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; EMT, Epithelial-to-mesenchymal transformation.

Herbal therapy and lung cancer

Based on data, the utilization of herbal therapy has been elevated in industrialized and developed societies. The reason for this

attention may be because of affordability, accessibility, safety, efficiency, low side effects, and likewise the acceptability of traditional products in these populations [45, 46]. A large

number of studies have addressed that the extracts from herbal remedies or mixtures can have anti-cancer effects against LC (Table 1.). For example, it is revealed that using the extract of *Scutellaria barbata* (*S. barbata*), a traditional herbal medicine, and leads to the inhibition of growth of LC cells by exerting cytotoxic and apoptotic effects. Another study by Al-Sheddi et al. indicated that the therapeutic effects of seed oil and seed extract of *Nigella sativa* (*N. sativa*) against human lung cancer cells through the reduction of viability of these cells [47, 48]. Also, Hwang et al. demonstrated that the use of *mountain ginseng* (*MG*) extract suppresses lung cancer cell growth through the suppression of NF- κ B nuclear translocation [49]. However, some plants have a potential for causing harmful effects, such as abdominal pains, diarrhea, vomiting, general weakness, drug interactions, and unsuitable formulations [45, 50]. Moreover, herbal remedies may also have more obstacles, for example, toxicity capacity, overdose potential, and little bioavailability of phytochemical agents in herbs [51]. Thus, using the capacity of herbal remedies with the maximum effectiveness and the minimum adverse impacts is a challenge yet. In this review study, we evaluated the curative aspects of some of the popular herbal products with low side effects, namely Curcumin, Green tea, quercetin, and *Marsdenia tenacissima*, [52-55] against LC.

Nanotechnology and lung cancer

Nowadays, there are multiple efforts in order to overcome the obstacles of herbal medicine for LC treatment. For example, various research has been carried out in order to improve the bioavailability of secondary metabolites, and among them, nano-based strategies had a promising outlook (Table 2.). Nanocarriers, like

polymeric NPs, liposomes, lipid NPs, and carbon dots, have indicated a positive role in enhancing curcumin bioavailability, and subsequently therapeutic capacity [56-59]. In order to treat diseases, like cancers, it is critical to realize the limitations to drugs, namely stabilization of curative agents in the environment of the living cell. Decreased drug efficiency may be in light of drug instability inside the cell, changes in cell-surface receptors, inaccessibility because of many chemical or targeting features of delivering molecules, up-regulation of efflux pumps, drug degradation, and signaling pathway changes with the development of disease [60, 61]. On the contrary, nano-biomolecules can be synthesized in order to increase bioavailability through the inhibition the drug absorption in the gastrointestinal tract and increase efficiency and decrease toxicity [62]. For instance, Quantum dots (QDs) have been assumed as one of the potential strategies for LC treatment [63]. QDs are semiconductor crystals in nanoscale that have several advantages, such as having a small diameter varying from 2 to 100 nm, considerable fluorescent quantum yields, and a high coefficient of absorption [64]. In an attempt to use nanotechnology against LC, it is shown that nano-sized neodymium oxide (Nano Nd₂O₃) can stimulate cell death, autophagy, and vacuolization in NSCLC cells. Neodymium is an infrequent earth element that has exhibited its cytotoxic impacts and apoptosis stimulation in some cancer cells [65]. In another effort, it is demonstrated that nanoplatin has pro-apoptotic influences on NSCLC cells by mediation of signaling pathways associated with P53. Plus, nanoplatin suppressed the proliferation of these cells in the study of Yiqun et al. [66]. silver nanoparticles (AgNPs) are other anticancer nanomaterials that its low concentration can

lead to chromosomal aberrations and DNA damage without a considerable toxicity [67]. It has been indicated that the use of AgNPs against human LC cell line can trigger apoptotic processes through increasing ROS. Thus, its combination with an antioxidant agent was recommended [68].

Curcumin and lung cancer

Curcumin (diferuloylmethane) is a phenolic compound which is found in rhizomes and roots of *Curcuma longa* (Linn) [69]. Curcumin has several bioactivities including anticancer, anti-inflammatory, neuroprotective, antioxidant, chemoprotective, anti-viral, anti-fungal, anti-depressant, metabolism modulating, antimicrobial, immuno-regulating, and antibiofilm production influences [70-74]. In molecular viewpoints, *curcumin*, as a pleiotropic molecule, regulates many targets, comprising involved transcription factor, such as NF- κ B, AP-1, STAT3, nuclear factor erythroid 2-related factor 2 (NRF-2), Hypoxia-inducible factor 1-alpha (HIF-1), and Peroxisome proliferator-activated receptor gamma (PPAR- γ); receptors, such as C-X-C chemokine receptor type 4 (CXCR-4), IL-8, and human epidermal growth factor receptor 2 (HER2); cytokines, such as Medical Care Plan (MCP), Macrophage inflammatory protein-1alpha (MIP-1alpha), IL, and Tumor necrosis factor (TNF); kinases, such as Janus kinase (JAK), Extracellular signal-regulated kinase (ERK), and epidermal growth factor receptor (EGFR); growth factors, such as Platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), Nerve growth factor (NGF), and Epidermal growth factor (EGF); and enzymes, such as Adenosine 5'-TriPhosphatase (ATPase), Glutathione S-transferases (GSTs), Nitric oxide synthases (iNOS), and Matrix

metalloproteinases (MMPs) [75, 76]. Furthermore, many studies have indicated that *curcumin* has an ability to exert more apoptotic effects in cancer cells in comparison with normal cells through the suppression of angiogenesis, receptor tyrosine kinase, nitric oxide synthase, and modulation of some transcriptional factors [77-79]. There is evidence indicating that *curcumin* can significantly suppress metastasis and invasion of tumoral agents [80-84]. In this line, *curcumin* stimulates cell apoptosis and autophagy and inhibits cell proliferation in LC by lysosomal pathway regulation and mitochondrial signaling pathway, which is dependent on ROS [85-87]. The inhibitory effects of curcumin have also been mentioned in other cancerous cells, like glioblastoma, oral cancer, colon cancer, and uterine leiomyosarcoma [88-92]. *Curcumin* can inhibit angiogenesis by suppressing The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathways (PI3K/Akt/mTOR) and activation of c-Met pathways [93]. It is possible that inhibitory impacts of *curcumin* on LC are mediated through the regulation of bcl-xL, bax, bcl-2, caspase-1, caspase-3, p53, and c-myc genes [94]. *Curcumin* also can improve the results of radiotherapy in LC by activation of different signaling pathways, for example, the EGF receptor [87]. According to the reports of WU et al, *curcumin* administration increases ROS, endoplasmic reticulum (ER) stress, and intracellular calcium in NSCLC [95]. It is said that *curcumin* not only affects MMP but also regulates the tumor inhibitor DnaJ-like heat shock protein (HLJ1), which can suppress the proliferation, invasion, motility, and progression of LC cells [84, 96]. Chen et al. showed that anti-metastasis and anti-invasive influences of *curcumin* are exerted through HLJ1 up-

regulation, and also *curcumin* can modulate the expression of HLJ1 via the JNK/JunD pathway and curb the metastasis and invasion of LC by the regulation of expression of E-cadherin (Figure 2.) [84]. *Curcumin* is also able to curb Sonic Hedgehog and Wnt/ β -catenin signaling activation and diminishes the expression of the marker of cancer stem cells (CSCs), such as Octamer-binding transcription factor 4 (Oct4), Nanog, Aldehyde Dehydrogenase 1 Family Member A1 (ALDH1), CD133, and CD44 [97]. Furthermore, it is addressed that exosomes, which act as vehicles for delivering anti-inflammatory factors, miRNAs, neural transmitters, and so on, from LC cells treated by *curcumin* have an anti-tumor function [98, 99]. Albeit there are many therapeutic and biological effects of *curcumin* administration, its potential in treating several disorders has been limited due to its weak bioavailability [100]. Low

absorption, fast excretion, and low solubility in water are considered as possible reasons for the low bioavailability of *curcumin* [87]. Additionally, *curcumin* has more stability in acidic circumstances than alkaline and natural circumstances [75]. Human and animal investigations have manifested the weak bioavailability of *curcumin* because of fast exertion and liver metabolism, and slight absorption in the gastrointestinal system [101]. It is addressed that Zinc nanoparticles loaded with curcumin (ZnO@Cur) have significant biocompatibility and exert remarkable cytotoxicity against human LC cells [56]. Zinc oxide nanoparticles (ZnO), which are named photocatalysts and semiconductors, stimulate cytotoxicity in proliferation and cell-dependent approach, as a result, dividing cancerous cells are mostly affected, and normal cells are rarely affected [57].

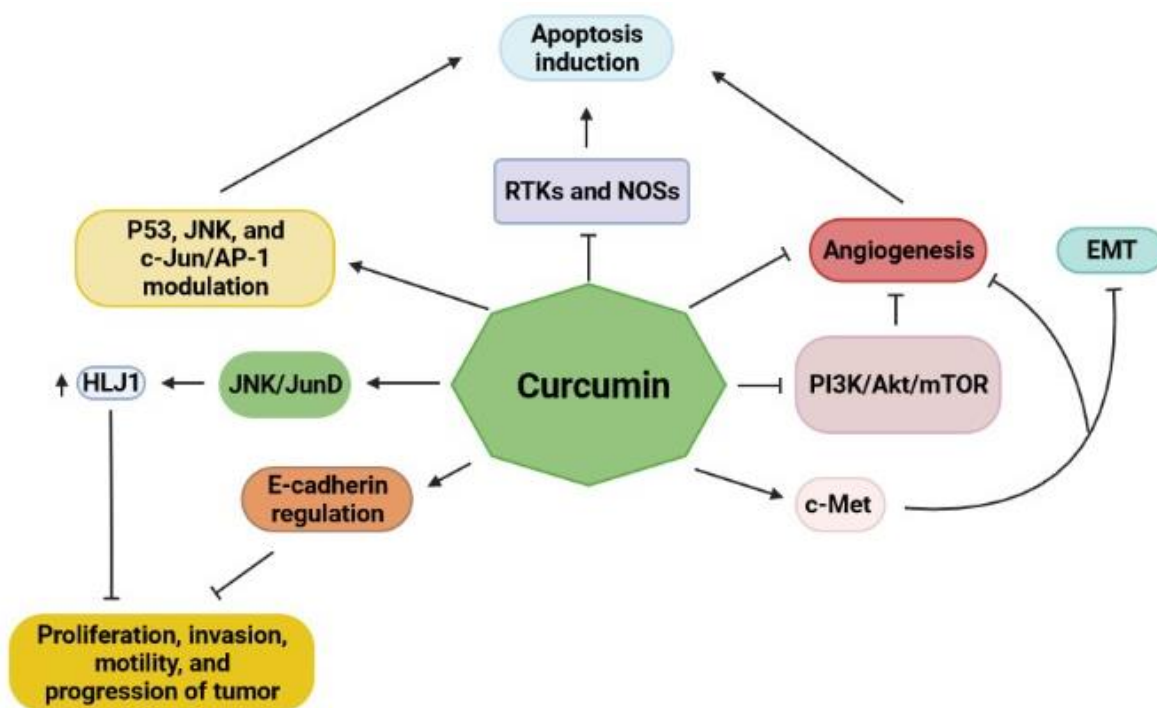


Fig. 2. Mechanism of action of *curcumin* against lung cancer. C-Met, Mesenchymal epithelial transition factor; EMT, Epithelial-to-mesenchymal transformation; RTKs, Receptor tyrosine kinases; NOSs, Nitric oxide synthases; and HLJ1, DnaJ-like heat shock protein.

Green tea and lung cancer

Green tea with scientific name of *Camellia sinensis* (L.) Kuntze, is an evergreen shrub and the most common drink after water [102]. The main anti-oxidative components of green tea comprise phenols, tannins, flavanols, catechins, and saponins [103]. Epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate are the main polyphenolic compounds in green tea [104]. Catechins have multiple advantageous features, such as anti-cancer, anti-inflammatory, anti-oxidative, anti-microbial, anti-obesity, hypotensive, and anti-diabetic properties [105]. Reports of animal and in vitro investigations indicated that green tea polyphenols have a protective role against LC by the anti-oxidative and antimutagenic features [106]. These polyphenols can also be effective against DNA damage resulted from carcinogenic agents and increase tumor cell apoptosis and curb angiogenesis [107]. Observational studies have mentioned a relationship between decreased cancer risk and the consumption of *green tea* [108]. Catechins, as an important constituent of *green tea*, stimulate the expression modification of miRs. The line with this notion, Zhong et al. express that catechins in *green tea* suppress the proliferation of LC cells through let-7 upregulation, which is a tumor inhibitor in lung malignancies [109]. Besides, it is implicated that the extract of *green tea* stimulates the expression of Annexin-1, a substantial anti-inflammatory factor. This factor can suppress the production of prostaglandin E₂ (PGE₂) and the expression of Cyclooxygenase-2 (COX-2). Elevated COX-2 expression has been demonstrated in NSCLC; furthermore, COX-2 increases PGE₂ formation, which is linked with various carcinogenic evidence, such as elevated angiogenesis, immune system inhibition, promotion of metastasis and invasion, and resistance to apoptosis (Figure 3.) [110, 111]. Green tea with the mediation of its polyphenols promotes the antiproliferative function of c-Met

and EGF receptor suppressor in NSCLC cells [112]. Sadava et al. examined the effect of epigallocatechin-3-gallate in LC cells resisted medication therapy. They declared that green tea administration diminishes telomerase and caspases 3, and caspase 8 activities, which is indicating apoptosis initiation and triggers DNA fragmentation [113]. Phenolic compounds present in green tea have also a potential for trapping ROS [114]. In spite of these beneficial effects against LC, some challenges concerning the utilization of extract of green tea have been represented, such as creating liver damages and its interactions with the performance of metabolic enzymes like Cytochrome P450 3A4 (CYP3A4) and UDP Glucuronosyltransferase Family 1 Member A1 (UGT1A1) [115]. Thus, finding a functional approach for modulating these adverse effects seems to be required. Shivaji et al. examined the therapeutic effects of nano-based herbal product, cadmium sulfide quantum dots (CdS QDs), by use of tea leaf extract (*Camellia sinensis*) against LC [58]. They observed that these CdS QDs can significantly suppress the growth of bacterial agents and have cytotoxic properties toward cancer cells of A549 compared with a group without QD treatment. Also, their analysis of fluorescence images manifested that CdS QDs stop the growth of A549 cells at the S phase of the cellular cycle [58]. Quantum dots have many benefits, for example, their size is less than 10 nm and has high biocompatibility and low cytotoxicity. Among QDs, CdS QDs can be synthesized through a wide range of chemical and physical methods, for instance, ultrasonic irradiation, microemulsion synthesis, and microwave heating [59]. By relying on the current studies, it could be declared that CdS QDs originated from biogenic synthesis have high levels of luminescence emission, outstanding quantum confinement impacts, and dramatic anti-microbial effects without serious adverse influences on the normal cells [59].

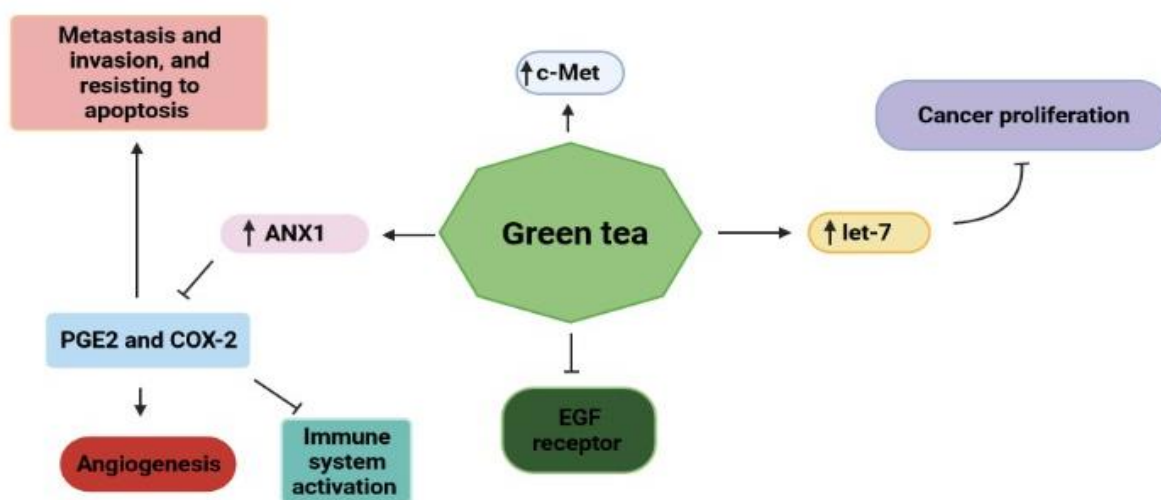


Fig. 3. Mechanism of action of green tea against lung cancer. C-Met, Mesenchymal epithelial transition factor; Let-7, lethal-7; ANX1, Annexin A1; PGE2, Prostaglandin E2; and COX-2, Cyclooxygenase-2.

Quercetin and lung cancer

Quercetin (3,30,40,5,7-pentahydroxyflavone) is considered as one of the natural polyphenolic agents which can mainly be found in several fruits and vegetables, for example, berries, capers, cranberry, fig, red onion, cranberry, asparagus, radish leaves, walnuts, coriander, and broccoli [116]. Quercetin has many pharmacological roles, such as anti-cancer, antiviral, antiplatelet, anti-obesity, antidiabetic, neuroprotective, and hepatoprotective actions [117, 118]. Quercetin has blocking impacts on the development of hepatic, gastric, rectum and colon carcinoma, ovarian and breast cancer [119]. This enriched-polyphenol source based on the cell type can arrest cell cycle at the transition of G1/S and/or G2/M [120]. Quercetin triggers the apoptotic event, and this occurrence may be mediated by some factors, such as microtubule disruption, stress proteins, Cox-2, NF- κ B, surviving, p53, Bcl-2 proteins, DNA topoisomerase II, heat shock proteins, caspase activation, and releasing cytochrome c [120]. Quercetin curbs the cells of breast cancer and melanoma through suppression of EMT and the

expression of MMP-9, respectively [121, 122]. In EMT, involved transcription factors, for example, Twist, Slug, ZEB, and Snail family chiefly inhibit E-cadherin expression [123]. Quercetin can reduce the protein levels of Slug and Snail in NSCLC cell lines [124]. Also, in lung cancer, quercetin is capable of inhibiting cancer cell growth through decreasing histone 3 phosphorylation (Figure 4.) [125]. Mukherjee et al. approved that quercetin can stimulate apoptosis in the cell line of NSCLC by mitochondrial depolarization through disbalance in the ratio of B-cell lymphoma 2 to Bcl2 antagonist X. They also declared that quercetin blocks the activity of NF- κ B, which in turn down-regulates the titer of IL-6 [126]. Quercetin administration may disassemble microtubules, microfilaments, and vimentin filaments and suppress N-cadherin expression in A549 NSCLC cells [127]. In spite of the advantageous effects of quercetin in medicine, it should be administrated as a high dose compound because of its low bioavailability [128]. As a result, finding a functional approach in order to better use quercetin is important.

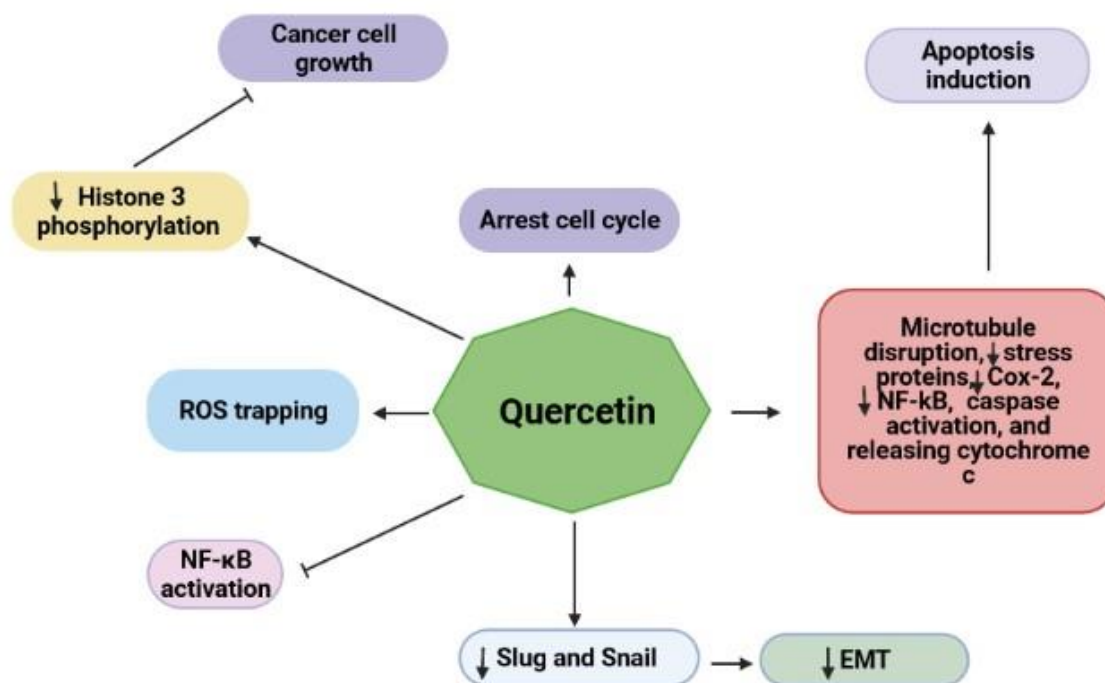


Fig. 4. Mechanism of action of *quercetin* against lung cancer. EMT, Epithelial-to-mesenchymal transformation; NF-κB, Nuclear factor kappa B; ROS, Reactive oxygen species; and COX-2, Cyclooxygenase-2.

Marsdenia tenacissima (Roxb.) Moon and lung cancer

Marsdenia tenacissima (*M. tenacissima*) is a medicinal traditional plant that belongs to the family of the *Asclepiadaceae* and is broadly found in subtropical and tropical regions in Asia [129]. It is manifested that *M. tenacissima* has anti-cancer, anti-inflammatory, and anti-asthmatic influences [130, 131]. Preliminary clinical evaluations have shown that *M. tenacissima* is useful for curing some cancers, such as lung, gastric, and esophageal cancer [132, 133]. *M. tenacissima* comprises polysaccharides, steroidal glycosides, organic acids, and other chemical ingredients. Among these components, C21 steroidal glycosides have a substantial role in tumor suppression by several mechanisms, for instance, defecting the proliferation and metastasis of cancer cell,

modulating signaling pathways, and having an inverse effect on multidrug resistance [134-136]. Furthermore, *M. tenacissima* through angiogenesis suppression, cell cycle arrest, and cell apoptosis stimulation can exert its anti-tumor impacts [137-139]. *M. tenacissima* is helpful in LC treatment by increased sensitivity of the chemotherapy and radiotherapy, diminished disadvantageous reactions, and enhanced life quality [140]. It is stated that *M. tenacissima* affects LC cell apoptosis via regulation of CALM1 transcription, which is encoding gene of calmodulin [141]. Research by Zhao et al. showed that the extract of *M. tenacissima* increases the accumulation of gefitinib in mice LC tissue through curbing ABCG2 activity, the main drug transporter to transport gefitinib [142]. Gefitinib is

characterized as the most principal subgroup of epidermal growth factor receptor tyrosine kinase suppressors, which take part in the first line of NSCLC by triggering the mutation of epidermal growth factor receptor [143]. Also, the results of Zhao et al. revealed that *M. tenacissima* extract suppresses liver CYPs, particularly CYP2D6 and CYP3A4, which are categorized as metabolizer enzymes of gefitinib (Figure 5.) [142, 144]. Jiao et al. manifested that *M. tenacissima* extract significantly suppresses the growth and induces apoptosis in NSCLC cells. They also mentioned that this herbal extract disrupts autophagic flux through upregulation of p62 and LC3-II expression which are assumed

as autophagic markers [145]. However, due to its significant cytotoxicity effects, it is stated that assessment of its clinical safety is urgent [134]. The line with this notion, some research indicated that *M. tenacissima* extract stimulates cytotoxicity and aging in erythrocytes by the increment of ROS and calcium levels [146]. So, increasing its curative efficacy through other techniques seems to be needed. A researcher, recently, studied the anti-cancer function of green synthesized gold NPs (AuNPs) from *M. tenacissima* on A549 cells. They concluded that these types of NPs trigger apoptosis and curb cell proliferation in A549 cell lines in a dose-dependent way.

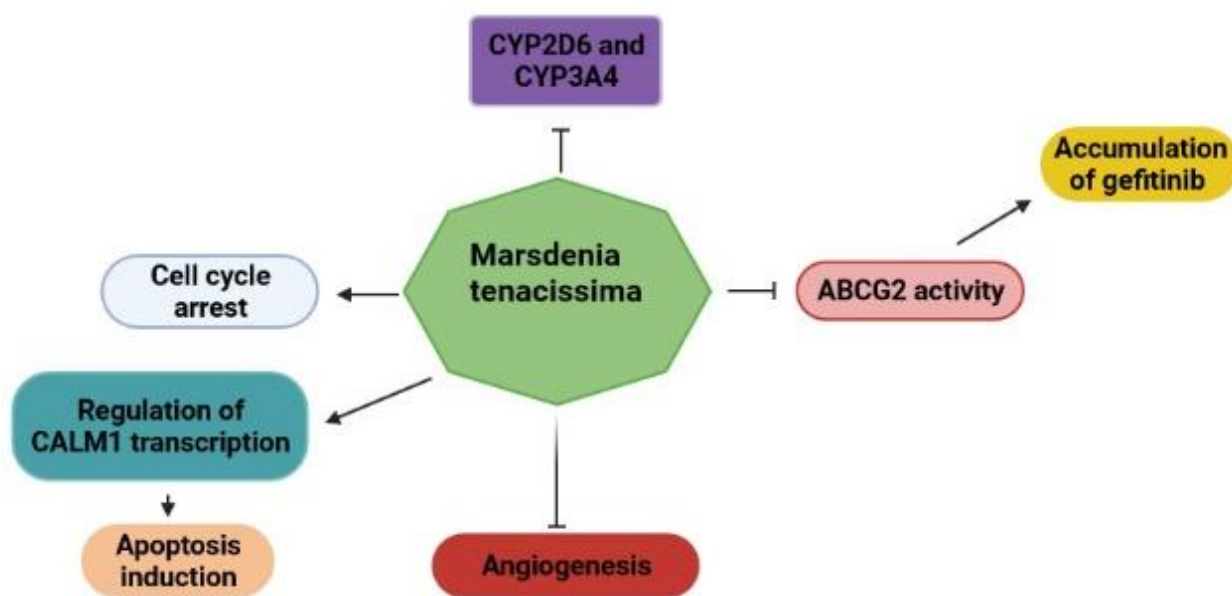


Fig. 5. Mechanism of action of *Marsdenia tenacissima* against lung cancer. ABCG2, ATP Binding Cassette Subfamily G Member 2; CALM1, Calmodulin 1; CYP2D6, Cytochrome P450 2D6; CYP3A4, Cytochrome P450 3A4.

Table 1. Anti-cancer effects of herbal products against lung cancer

Herbal products	Dosage	Mechanism	in vivo/in vitro	references
Curcumin	100 or 300 mg/kg	Inhibition of EMT and angiogenesis	in vivo/in vitro	[93]
Curcumin	0–160 μ M	Cell growth inhibition and apoptosis induction	in vitro	[94]
Curcumin	25 μ M	Increase of ROS and apoptosis induction	in vitro	[95]
Curcumin	5, 10, 20, and 40 μ M	Cell proliferation inhibition and apoptosis induction	in vitro	[97]
Curcumin	20 μ M	Inhibition of colony formation and cell proliferation	in vivo/in vitro	[147]
Curcumin	100 μ M	Cell proliferation inhibition and apoptosis promotion	in vivo/in vitro	[148]
Curcumin	100 mg/kg	Inhibition of angiogenesis and cell migration	in vivo/in vitro	[149]
<i>Camellia sinensis</i>	25–50 μ M	Cell growth suppression and cell proliferation inhibition	in vitro	[150]
<i>Camellia sinensis</i>	70 μ M	Telomerase inhibition and apoptosis induction	in vitro	[113]
<i>Camellia sinensis</i>	20 and 40 mg/kg	Apoptosis induction and cell motility reduction	in vitro	[151]
<i>Camellia sinensis</i>	15 mg/kg	Inhibition of cell growth and cell proliferation	in vivo/in vitro	[112]
<i>Camellia sinensis</i>	10, 20, and 40 μ g	Inhibition of COX-2 expression and ANX1 induction	in vitro	[110]
<i>Camellia sinensis</i>	50, 100, and 200 μ g	Inhibition of cell proliferation and cell growth	in vitro	[109]
Quercetin	1–100 μ M	Inhibition of cell migration, cell motility, and EMT	in vivo/in vitro	[124]
Quercetin	0–200 μ M	Apoptosis induction and the inhibition of cellular proliferation	in vitro	[152]
Quercetin	8, 4 and 2 mg/kg	Apoptosis induction and cell growth inhibition	in vivo/in vitro	[153]
Quercetin	200 μ g	Apoptosis induction, cell proliferation, and growth inhibition	in vivo/in vitro	[57]
Quercetin	10, 50, and 200 μ M	Cell viability reduction and HSP70 expression suppression	in vitro	[56]
Quercetin	10 – 100 μ M	Apoptosis induction and p-STAT3 expression inhibition	in vitro	[126]
<i>M. tenacissima</i>	20 and 100 ml	Apoptosis induction and cell growth suppression	in vitro	[58]
<i>M. tenacissima</i>	5, 10, 20 g/kg	Gefitinib level elevation and reduction of CYPs activity	in vivo	[142]
<i>M. tenacissima</i>	200 mL	Apoptosis induction and autophagic flux disruption	in vitro	[145]
<i>M. tenacissima</i>	5g/kg	EGFR suppression and EMT inhibition	in vivo/in vitro	[59]

Table 2. Anti-cancer effects of nano-based herbal products against lung cancer

Nano-based herbal product	Dosage	Mechanism	in vivo/in vitro	references
ZnO@Cur NPs	0.78-25 μ M	Apoptosis induction and cell migration inhibition	in vitro	[154]
Cur-PLGA-NPs	10, 20, and 30 μ M	Inhibition of colony formation and cell migration	in vitro	[155]
CURM	0-12.5 μ g/ml	Cell proliferation inhibition and increase of antioxidant activity	in vitro	[156]
Nano-EGCG	0-10 μ M	Cell growth inhibition and colony formation suppression	in vitro	[157]
CdS QDs of tea	10, 25, and 50 μ g/mL	Apoptosis induction and cell growth inhibition	in vitro	[57]
Cet-QUE NPs	0-32 μ g/mL	Apoptosis induction and cell growth inhibition	in vitro/in vivo	[58]
QUR-M	0-32 μ g/mL	Apoptosis induction and cell proliferation inhibition	in vitro	[59]
AuNPs from <i>M. tenacissima</i>	2.5- 25 μ g/ml	Apoptosis induction and cell growth inhibition	in vitro	[158]

5. Conclusion

Herbal medicine, especially using *Curcumin*, *Green tea*, *quercetin*, and *Marsdenia tenacissima*, can be a good candidate for LC treatment through affecting some key mechanisms that are important in LC pathogenesis, for example, arresting cell cycle, suppressing inflammation, angiogenesis, EMT, and MMP-9, modulating the immune system and involved transcription factors (e.g., NF- κ B, STAT3, and NRF-2), and inducing cell apoptosis and autophagy. However, herbal remedies have some limitations and may result in harmful impacts by increasing ROS, intracellular calcium, which in turn lead to cytotoxicity. Moreover, they may have low bioavailability, low absorption, and fast excretion. Among these, it seems that using

some nanocarriers, like Zinc oxide NPs, CdS QDs, NPs conjugated with Cet, and AuNPs from herbal products can significantly solve the limitation of herbal medicine and increase its efficacy against LC. However, more investigations with large sample sizes on other nano-and herbal nanoformulations in vivo and in vitro are required to validate our findings.

Author contributions

M. Y Designed and draft the manuscript; J. M, R. G and R.G drafted the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Woodman C, Vundu G, George A and Wilson CM. Applications and strategies in nanodiagnosis and nanotherapy in lung cancer. *Seminars in Cancer Biology* 2021; 69: 349-364. doi: 10.1016/j.semcancer.2020.02.009.
2. Asakura K, Kadota T, Matsuzaki J, Yoshida Y, Yamamoto Y, Nakagawa K, Takizawa S, Aoki Y, Nakamura E, Miura J, Sakamoto H, Kato K, Shun-ichi Watanabe Shi and Takahiro Ochiya. A miRNA-based diagnostic model predicts resectable lung cancer in humans with high accuracy. *Commun. Biol* 2020; 3(134): 1-9. doi: 10.1038/s42003-020-0863-y.
3. Tao S-L, Wang X-m, Feng Y-g, Kang P-m, Li Q-y, Sun T-y, Tan Q-y and Deng B. Is the presence of lung injury in COVID-19 an independent risk factor for secondary lung cancer? *Med. Hypotheses* 2020; 143: 110074. doi: 10.1016/j.mehy.2020.110074.
4. Naeli P, Yousefi F, Ghasemi Y, Savardashtaki A and Mirzaei H. The role of microRNAs in lung cancer: implications for diagnosis and therapy. *Curr. Mol. Med.* 2020; 20: 90-101. doi: 10.2174/1566524019666191001113511.
5. Zappa C and Mousa SA. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res.* 2016; 5(3): 288-300. doi: 10.21037/tlcr.2016.06.07.
6. Van Meerbeeck CMO JP, Fennell FRCP DA and De Ruyscher MD DK. Small-cell lung cancer. *The Lancet* 2011; 378(9804): 1741-1755. doi: 10.1016/S0140-6736(11)60165-7.
7. Xu Q, Shi NJ, Zhang H and Zhu YM. Effects of combined general-epidural anesthesia and total intravenous anesthesia on cellular immunity and prognosis in patients with non-small cell lung cancer: A comparative study. *Mol. Med. Rep.* 2017; 16(4): 4445-4454. doi: 10.3892/mmr.2017.7144.
8. Moya-Horno I, Viteri S, Karachaliou N and Rosell R. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). *Ther. Adv. Med. Oncol* 2018; 10: 1-27. doi: 10.1177/1758834017745012.
9. Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, Yin J, Zhan Ch and Wang Q. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res.* 2019; 11: 943-953. doi: 10.2147/CMAR.S187317.
10. Shu Y, Zhu L, Yuan F, Kong X, Huang T and Cai Y-D. Analysis of the relationship between PM2. 5 and lung cancer based on protein-protein interactions. *Comb. Chem. High Throughput Screen* 2016; 19(2): 100-108. doi: 10.2174/1386207319666151110123345.
11. Patel AM and Peters SG. Clinical manifestation of lung cancer. *Mayo Clin. Pro.* 1993; 68(3): 273-277. doi: 10.1016/s0025-6196(12)60049-4.
12. An Q, Shi C-X, Guo H, Xie S-M, Yang Y-Y, Liu Y-N, Liu Z-H, Zhou Ch-ZH and Niu F-J. Development and characterization of octreotide-modified curcumin plus docetaxel micelles for potential treatment of non-small-cell lung cancer. *Pharm. Dev. Technol.* 2019; 24(9): 1164-1174. doi: 10.1080/10837450.2019.1647236.
13. Xie J, Zhuan B, Wang H, Wang Y, Wang X, Yuan Q and Yang Z. Huaier extract suppresses non-small cell lung cancer progression through activating NLRP3-dependent pyroptosis. *Anat. Rec.* 2019; 304(2): 291-301. doi: 10.1002/ar.24307.
14. Ahn J, Kim H and Yang KM. An aqueous extract of a bifidobacterium species induces apoptosis and inhibits invasiveness of non-small cell lung cancer cells. *J. Microbiol. Biotechnol.*

- 2020; 30(6): 885-893. doi: 10.4014/jmb.1912.12054.
- 15.** Liu J, Liu X, Dong M, Zhao H, Li M, Zhang H, Ji H, Shi Y, Cui Y, Wu D, Chen G and Chen J. Symptom trajectories during chemotherapy in patients with non-small cell lung cancer (NSCLC) and the function of prolonging low dose dexamethasone in promoting enhanced recovery after chemotherapy. *Thorac. Cancer* 2021; 12(6): 783-795. doi: 10.1111/1759-7714.13830.
- 16.** Sajadimajd S, Bahramsoltani R, Iranpanah A, Patra JK, Das G, Gouda S, Rahimi R, Rezaei-amiri E, Cao H, Giampieri F, Battino M, Tundis R, Campos MG, Farzaei MH and Xiao J. Advances on natural polyphenols as anticancer agents for skin cancer. *Pharmacol. Res* 2020; 151: 104584. doi: 10.1016/j.phrs.2019.104584.
- 17.** Farzaei MH, Bahramsoltani R and Rahimi R. Phytochemicals as adjunctive with conventional anticancer therapies. *Curr. Pharm. Des.* 2016; 22(27): 4201-4018. doi: 10.2174/1381612822666160601100823.
- 18.** Kwon C-Y, Lee B, Kim K-I and Lee B-J. Herbal medicine on cancer-related fatigue of lung cancer survivors: Protocol for a systematic review. *Medicine* 2020; 99(5): e18968. doi: 10.1097/MD.00000000000018968.
- 19.** Ernest U, Chen H-Y, Xu M-J, Davatgaran Taghipour Y, Asad MHHB, Rahimi R and Murtaza G. Anti-cancerous potential of polyphenol-loaded polymeric nanotherapeutics. *Molecules* 2018; 23(11): 1-21. doi: 10.3390/molecules23112787.
- 20.** Mukherjee A, Paul M and Mukherjee S. Recent progress in the theranostics application of nanomedicine in lung cancer. *Cancers* 2019; 11(5): 1-18. doi: 10.3390/cancers11050597.
- 21.** Forgacs E, Zöchbauer-Müller S, Oláh E and Minna JD. Molecular genetic abnormalities in the pathogenesis of human lung cancer. *Pathol. Oncol. Res.* 2001; 7: 6-13. doi: 10.1007/BF03032598.
- 22.** Burstein HJ and Schwartz RS. Molecular origins of cancer. *N. Engl. J. Med.* 2008; 358(5): 527. doi: 10.1056/NEJMe0800065.
- 23.** Cho WC, Kwan CK, Yau S, So PP, Poon PC and Au JS. The role of inflammation in the pathogenesis of lung cancer. *Expert Opin. Ther. Targets* 2011; 15(9): 1127-1137. doi: 10.1517/14728222.2011.599801.
- 24.** Garon EB, Yang JC-H and Dubinett SM. The role of interleukin 1 β in the pathogenesis of lung cancer. *JTO Clin. Res. Rep.* 2020; 1(1): 1-11. doi: 10.1016/j.jtocrr.2020.100001.
- 25.** Azad N, Rojanasakul Y and Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. *J. Toxicol. Environ. Health, Part B Crit. Rev.* 2008; 11(1): 1-15. doi: 10.1080/10937400701436460.
- 26.** Li R, Ong SL, Tran LM, Jing Z, Liu B, Park SJ, Huang ZL, Walser TC, Heinrich EL, Lee G, Salehi-Rad R, Crosson WP, Pagano PC, Paul MK, Xu Sh, Herschman H, Krysan K and Dubinett S. Chronic IL-1 β -induced inflammation regulates epithelial-to-mesenchymal transition memory phenotypes via epigenetic modifications in non-small cell lung cancer. *Sci. Rep.* 2020; 10(377). doi: 10.1038/s41598-019-57285-y.
- 27.** Kundu JK and Surh Y-J. Inflammation: gearing the journey to cancer. *Mutat. Res.* 2008; 659(1-2): 15-30. doi: 10.1016/j.mrrev.2008.03.002.
- 28.** El-Kenawi A and Ruffell B. Inflammation, ROS, and mutagenesis. *Cancer Cell.* 2017; 32(6): 727-729. doi: 10.1016/j.ccell.2017.11.015.
- 29.** Poillet-Perez L, Despouy G, Delage-Mourroux R and Boyer-Guittaut M. Interplay between ROS and autophagy in cancer cells, from tumor initiation to cancer therapy. *Redox*

- Biol.* 2015; 4: 184-92. doi: 10.1016/j.redox.2014.12.003.
- 30.** Wu D, Liu J, Chen J, He H, Ma H and Lv X. miR-449a suppresses tumor growth, migration, and invasion in non-small cell lung cancer by targeting a HMGB1-Mediated NF- κ B signaling pathway. *Oncol. Res.* 2019; 27(2): 227-35. doi: 10.3727/096504018X15213089759999.
- 31.** DB Vendramini-Costa and Carvalho JE. Molecular link mechanisms between inflammation and cancer. *Curr. Pharm. Des.* 2012; 18(26): 3831-3852. doi: 10.2174/138161212802083707.
- 32.** Li R, Zhou R and Zhang J. Function of PM2.5 in the pathogenesis of lung cancer and chronic airway inflammatory diseases. *Oncol. Lett.* 2018; 15(5): 7506-7514. doi: 10.3892/ol.2018.8355.
- 33.** Marshall EA, Ng KW, Kung SH, Conway EM, Martinez VD, Halvorsen EC, Rowbotham DA, Vucic EA, Plumb AW, Becker-Santos DD, Enfield KSS, Kennett JY, Bennewith KL, Lockwood WW, Lam S, English JC, Abraham N and Lam WL. Emerging roles of T helper 17 and regulatory T cells in lung cancer progression and metastasis. *Mol. Cancer* 2016; 15: 1-15. doi: 10.1186/s12943-016-0551-1.
- 34.** Narendra BL, Reddy KE, Shantikumar S and Ramakrishna S. Immune system: a double-edged sword in cancer. *Inflamm. Res.* 2013; 62: 823-834. doi: 10.1007/s00011-013-0645-9.
- 35.** Eisenstein EM and Williams CB. The T reg/Th17 Cell Balance: A New Paradigm for Autoimmunity. *Pediatr. Res.* 2009; 65: 26-31. doi: 10.1203/PDR.0b013e31819e76c7.
- 36.** Lin S, Zhen Y, Guan Y and Yi H. Roles of Wnt/ β -catenin signaling pathway regulatory long non-coding RNAs in the pathogenesis of non-small cell lung cancer. *Cancer Manag. Res.* 2020; 12: 4181-4191. doi: 10.2147/CMAR.S241519.
- 37.** Chen W, Li Z, Bai L and Lin Y. NF- κ B, a mediator for lung carcinogenesis and a target for lung cancer prevention and therapy target. *FBL.* 2011; 16(3): 1172-1185. doi: 10.2741/3782.
- 38.** Larsen JE, Nathan V, Osborne JK, Farrow RK, Deb D, Sullivan JP, Dospoy PD, Augustyn A, Hight SK, Sato M, Girard L, Behrens C, Wistuba II, Gazdar AF, Hayward NK and Minna JD. ZEB1 drives epithelial-to-mesenchymal transition in lung cancer. *J. Clin. Invest.* 2016; 126(9): 3219-3235. doi: 10.1172/JCI76725.
- 39.** Dutta P, Sabri N, Li J and Li WX. Role of STAT3 in lung cancer. *JAK-STAT* 2014; 3(4): e999503. 1-9. doi: 10.1080/21623996.2014.999503.
- 40.** Rapp J, Jaromi L, Kvell K, Miskei G and Pongracz JE. WNT signaling–lung cancer is no exception. *Respir. Res.* 2017; 18(167): 1-16. doi: 10.1172/JCI76725.
- 41.** Ryter SW and Choi AM. Autophagy in lung disease pathogenesis and therapeutics. *Redox Biol.* 2015; 4: 215-225. doi: 10.1016/j.redox.2014.12.010.
- 42.** Shivapurkar N, Reddy J, Chaudhary PM and Gazdar AF. Apoptosis and lung cancer: a review. *J. Cell. Biochem.* 2003; 88(5): 885-98. doi: 10.1002/jcb.10440.
- 43.** Liu G, Pei F, Yang F, Li L, Amin AD, Liu S and Cho WC. Role of autophagy and apoptosis in non-small-cell lung cancer. *Int. J. Mol. Sci.* 2017; 18(2): 367. doi: 10.3390/ijms18020367.
- 44.** Musial C, Zaucha R, Kuban-Jankowska A, Konieczna L, Belka M, Gammazza AM Baczek T, Cappello F, Wozniak M and Gorska-Ponikowska M. Plausible role of estrogens in pathogenesis, progression and therapy of lung

- cancer. *Int. J. Environ. Res. Public Health* 2021; 18(2): 648. doi: 10.3390/ijerph18020648.
- 45.** Duru CB, Uwakwe KA, Chinomso NC, Mbachi II, Diwe KC, Agunwa CC, IWU AC and Merenu IA. Socio-demographic determinants of herbal medicine use in pregnancy among Nigerian women attending clinics in a tertiary Hospital in Imo State, south-east, Nigeria. *Am. J. Med. Stud.* 2016; 4(1): 1-10. doi: 10.12691/ajms-4-1-1.
- 46.** Kamboj VP. Herbal medicine. *Curr. Sci.* 2000; 78: 35-39.
- 47.** Yin X, Zhou J, Jie C, Xing D and Zhang Y. Anticancer activity and mechanism of *Scutellaria barbata* extract on human lung cancer cell line A549. *Life Sci.* 2004; 75(18): 2233-2244. doi: 10.1016/j.lfs.2004.05.015.
- 48.** Al-Sheddi ES, Farshori NN, Al-Oqail MM, Musarrat J, Al-Khedhairy AA and Siddiqui MA. Cytotoxicity of *Nigella sativa* seed oil and extract against human lung cancer cell line. *Asian Pac. J. Cancer Prev.* 2014; 15(2): 983-987. doi: 10.7314/apjcp.2014.15.2.983.
- 49.** Hwang JW, Oh JH, Yoo H-S, Lee Y-W, Cho C-K, Kwon K-R, Yoon J-H, Park J, Her S, Lee Z-W, Jang I-S and Choi J-S. Mountain ginseng extract exhibits anti-lung cancer activity by inhibiting the nuclear translocation of NF- κ B. *Am. J. Chin. Med.* 2012; 40(1): 187-202. doi: 10.1142/S0192415X12500152.
- 50.** Tchacondo T, Karou SD, Batawila K, Agban A, Ouro-Bang'na K, Anani KT, Gbeassor M, de Souza C. Herbal remedies and their adverse effects in Tem tribe traditional medicine in Togo. *Afr. J. Tradit. Complement. Altern. Med.* 2011; 8(1): 45-60. doi: 10.4314/ajtcam.v8i1.60522.
- 51.** Khogta S, Patel J, Barve K and Londhe V. Herbal nano-formulations for topical delivery. *J. Herb. Med.* 2020; 20: 1-12. doi: 10.1016/j.hermed.2019.100300.
- 52.** Sharifi S, Fathi N, Memar MY, Hosseiniyan Khatibi SM, Khalilov R, Negahdari R, Zununi Vahed S and Dizaj SM. Anti-microbial activity of curcumin nanoformulations: New trends and future perspectives. *Phytother. Res.* 2020; 34(8): 1926-1946. doi: 10.1002/ptr.6658.
- 53.** Chen I-J, Liu C-Y, Chiu J-P and Hsu C-H. Therapeutic effect of high-dose green tea extract on weight reduction: A randomized, double-blind, placebo-controlled clinical trial. *Clin. Nutr.* 2016; 35(3): 592-599. doi: 10.1016/j.clnu.2015.05.003.
- 54.** Batiha GE-S, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, Algammal AM and Elewa YHA. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. *Foods* 2020; 9(3): 1-16. doi: 10.3390/foods9030374.
- 55.** Zhou X, Liu M, Ren Q, Zhu W, Wang Y, Chen H and Chen J. Oral and injectable *Marsdenia tenacissima* extract (MTE) as adjuvant therapy to chemotherapy for gastric cancer: a systematic review. *BMC Complement Altern. Med* 2019; 19(1): 1-14. doi: 10.1186/s12906-019-2779-y.
- 56.** Naoshad M, Darksha U, Tarique M, Huma N, Ashraf M, Ramesh R, Shams T, Torki A-Z, Ahdab A, Israa J-H and Mohd S. The Role of Natural Products and Their Multitargeted Approach to Treat Solid Cance. *Cells.* 2022; 11(14): 1-20. doi: 10.3390/cells11142209.
- 57.** Shivaji K, Mani S, Ponmurugan P, De Castro CS, Lloyd Davies M, Balasubramanian MG and Pitchaimuthu S. Green-synthesis-derived CdS quantum dots using tea leaf extract: antimicrobial, bioimaging, and therapeutic applications in lung cancer cells. *ACS Appl. Nano Mater.* 2018; 1(4): 1683-1693. doi: 10.1021/acsanm.8b00147.

- 58.** Wang Y, Yu H, Wang S, Gai C, Cui X, Xu Z, Li W and Zhang W. Targeted delivery of quercetin by nanoparticles based on chitosan sensitizing paclitaxel-resistant lung cancer cells to paclitaxel. *Mater. Sci. Eng: C Mater Biol. Appl.* 2021; 119: 1-9. doi: 10.1016/j.msec.2020.111442.
- 59.** Han S-Y, Zhao W, Han H-B, Sun H, Xue D, Jiao Y-N, He X-R, Jiang S-T and Li P-P. *Marsdenia tenacissima* extract overcomes Axl- and Met-mediated erlotinib and gefitinib cross-resistance in non-small cell lung cancer cells. *Oncotarget* 2017; 8: 56893-56905. doi: 10.18632/oncotarget.18137.
- 60.** Grady WM. Epigenetic events in the colorectum and in colon cancer. *Biochem. Soc. Trans.* 2005; 33: 684-688. doi: 10.1042/BST0330684.
- 61.** Rehman Q, Akash MSH, Rasool MF and Rehman K. Role of kinetic models in drug stability. *Drug Stability and Chemical Kinetics*: Springer; 2020. P: 155-65. doi: 10.1007/978-981-15-6426-0_11.
- 62.** Simos YV, Spyrou K, Patila M, Karouta N, Stamatis H, Gournis D, Dounousi E and Peschos D. Trends of nanotechnology in type 2 diabetes mellitus treatment. *Asian J. Pharm. Sci.* 2021; 16(1): 62-76. doi: 10.1016/j.ajps.2020.05.001.
- 63.** Riyaz B, Sudhakar K and Mishra V. Quantum dot-based drug delivery for lung cancer. *Nanotechnology-Based Targeted Drug Delivery Systems for Lung Cancer*: Elsevier; 2019. P: 311-26. doi: 10.1016/B978-0-12-815720-6.00013-7.
- 64.** Ruzycka-Ayoush M, Kowalik P, Kowalczyk A, Bujak P, Nowicka AM, Wojewodzka M, Kruszewski M and Grudzinski IP. Quantum dots as targeted doxorubicin drug delivery nanosystems in human lung cancer cells. *Cancer Nanotechnol.* 2021; 12: 1-27. doi: 10.1186/s12645-021-00080-0.
- 65.** Chen Y, Yang L, Feng C and Wen L-P. Nano neodymium oxide induces massive vacuolization and autophagic cell death in non-small cell lung cancer NCI-H460 cells. *Biochem. Biophys. Res. Commun.* 2005; 337(1): 52-60. doi: 10.1016/j.bbrc.2005.09.018.
- 66.** Liu Y, Hu F and Zhao L. Effect of Nano-Platinum on Proliferation and Apoptosis of Non-Small Cell Lung Cancer Cells via P53 Pathway. *J. Nanosci. Nanotechnol* 2021; 21(2): 903-908. doi: 10.1166/jnn.2021.18629.
- 67.** Gurunathan S, Qasim M, Park C, Yoo H, Kim J-H and Hong K. Cytotoxic potential and molecular pathway analysis of silver nanoparticles in human colon cancer cells HCT116. *Int. J. Mol. Sci* 2018; 19(8): 2269. 1-19. doi: 10.3390/ijms19082269.
- 68.** Foldbjerg R, Dang DA and Autrup H. Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549. *Arch. Toxicol* 2011; 85(7): 743-750. doi: 10.1007/s00204-010-0545-5.
- 69.** Bahramsoltani R, Rahimi R and Farzaei MH. Pharmacokinetic interactions of curcuminoids with conventional drugs: A review. *J. Ethnopharmacol.* 2017; 209: 1-12. doi: 10.1016/j.jep.2017.07.022.
- 70.** Yang Q-Q, Farha AK, Kim G, Gul K, Gan R-Y and Corke H. Antimicrobial and anticancer applications and related mechanisms of curcumin-mediated photodynamic treatments. *Trends Food Sci. Technol.* 2020; 97: 341-54. doi: 10.1016/j.tifs.2020.01.023.
- 71.** Stohs SJ, Chen O, Ray SD, Ji J, Bucci LR and Preuss HG. Highly bioavailable forms of curcumin and promising avenues for curcumin-based research and application: A review. *Molecules* 2020; 25(6): 1-12. doi: 10.3390/molecules25061397.

72. Farzaei MH, Zobeiri M, Parvizi F, El-Senduny FF, Marmouzi I, Coy-Barrera E, Naseri R, Nabavi SM, Rahimi R and Abdollahi M. Curcumin in liver diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. *Nutrients* 2018; 10(7): 1-28. doi: 10.3390/nu10070855.
73. Mehraban MSA, Tabatabaei-Malazy O, Rahimi R, Daniali M, Khashayar P and Larijani B. Targeting dyslipidemia by herbal medicines: A systematic review of meta-analyses. *J. Ethnopharmacol.* 2021; 280: 114407. doi: 10.1016/j.jep.2021.114407.
74. Roghani-Shahraki H, Karimian M, Valipour S, Behjati M, Arefnezhad R and Mousavi A. Herbal therapy as a promising approach for regulation on lipid profiles: A review of molecular aspects. *J. Cell. Physiol.* 2021; 236(8): 5533-5546. doi: 10.1002/jcp.30282.
75. Goel A, Kunnumakkara AB and Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem. Pharmacol.* 2008; 75(4): 787-809. doi: 10.3390/molecules25061397.
76. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB and Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett.* 2008; 267(1): 133-164. doi: 10.1016/j.canlet.2008.03.025.
77. Kim S-Y, Jung S-H and Kim H-S. Curcumin is a potent broad spectrum inhibitor of matrix metalloproteinase gene expression in human astrogloma cells. *Biochem. Biophys. Res. Communications* 2005; 337(2): 510-516. doi: 10.1016/j.bbrc.2005.09.079.
78. Singh M and Singh N. Curcumin counteracts the proliferative effect of estradiol and induces apoptosis in cervical cancer cells. *Mol. Cell. Biochem.* 2011; 347: 1-11. doi: 10.1007/s11010-010-0606-3.
79. Yu T, Li J, Qiu Y and Sun H. 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) facilitates curcumin-induced melanoma cell apoptosis by enhancing ceramide accumulation, JNK activation, and inhibiting PI3K/AKT activation. *Mol. Cell. Biochem.* 2012; 361: 47-54. doi: 10.1007/s11010-011-1086-9.
80. Ji C, Cao C, Lu S, Kivlin R, Amaral A, Kouttab N, Yang H, Chu W, Bi Z, Di W and Wan Y. Curcumin attenuates EGF-induced AQP3 up-regulation and cell migration in human ovarian cancer cells. *Cancer Chemother Pharmacol* 2008; 62(5): 857-865. doi: 10.1007/s00280-007-0674-6.
81. Lin S-S, Lai K-C, Hsu S-C, Yang J-S, Kuo C-L, Lin J-P, Ma Y-S, Wu C-C and Chung J-G. Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and-9 and Vascular Endothelial Growth Factor (VEGF). *Cancer Lett.* 2009; 285(2): 127-133. doi: 10.1016/j.canlet.2009.04.037.
82. Chen Q-y, Zheng Y, Jiao D-m, Chen F-y, Hu H-z, Wu Y-q, Song J, Yan J, Wu L-j and Lv G-y. Curcumin inhibits lung cancer cell migration and invasion through Rac1-dependent signaling pathway. *J. Nutr. Biochem.* 2014; 25(2): 177-185. doi: 10.1016/j.jnutbio.2013.10.004.
83. Chen Q-y, Jiao D-m, Wang L-f, Wang L, Hu H-z, Song J, Yan J, Wu L-j and Shi J-g. Curcumin inhibits proliferation-migration of NSCLC by steering crosstalk between a Wnt signaling pathway and an adherens junction via EGR-1. *Mol. Biosyst.* 2015; 11(3): 859-868. doi: 10.1039/C4MB00336E.
84. Chen H-W, Lee J-Y, Huang J-Y, Wang C-C, Chen W-J, Su S-F, Huang C-W, Ho C-C, Chen JWJ, Tsai M-F, Yu S-L and Yang P-C. Curcumin inhibits lung cancer cell invasion and

- metastasis through the tumor suppressor HLJ1. *Cancer Res.* 2008; 68(18): 7428-7438. doi: 10.1158/0008-5472.CAN-07-6734.
- 85.** Chen Q, Wang Y, Xu K, Lu G, Ying Z, Wu L, Zhan J, Fang R, Wu Y and Zhou J. Curcumin induces apoptosis in human lung adenocarcinoma A549 cells through a reactive oxygen species-dependent mitochondrial signaling pathway. *Oncol. Rep.* 2010; 23(2): 397-403. doi: 10.1016/j.bcp.2005.04.026.
- 86.** Chen Q-Y, Shi J-G, Yao Q-H, Jiao D-M, Wang Y-Y, Hu H-Z, Wu Y-Q, Song J, Yan J and Wu L-J. Lysosomal membrane permeabilization is involved in curcumin-induced apoptosis of A549 lung carcinoma cells. *Mol. Cell. Biochem.* 2012; 359(1-2): 389-398. doi: 10.1007/s11010-011-1033-9.
- 87.** Ashrafizadeh M, Najafi M, Makvandi P, Zarrabi A, Farkhondeh T and Samarghandian S. Versatile role of curcumin and its derivatives in lung cancer therapy. *J. Cell. Physiol.* 2020; 235(12): 9241-9268. doi: 10.1002/jcp.29819.
- 88.** Lee YJ, Kim N-Y, Suh Y-A and Lee C. Involvement of ROS in curcumin-induced autophagic cell death. *Korean J. Physiol. Pharmacol.* 2011; 15(1): 1-7. doi: 10.4196/kjpp.2011.15.1.1.
- 89.** Kim JY, Cho TJ, Woo BH, Choi KU, Lee CH, Ryu MH and Park HR. Curcumin-induced autophagy contributes to the decreased survival of oral cancer cells. *Arch. Oral Biol.* 2012; 57(8): 1018-1025. doi: 10.1016/j.archoralbio.2012.04.005.
- 90.** Zhuang W, Long L, Zheng B, Ji W, Yang N, Zhang Q and Liang Z. Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy. *Cancer Sci.* 2011; 103(4): 684-690. doi: 10.1111/j.1349-7006.2011.02198.x.
- 91.** Li B, Takeda T, Tsuiji K, Wong TF, Tadakawa M, Kondo A, Nagase S and Yaegashi N. Curcumin induces cross-regulation between autophagy and apoptosis in uterine leiomyosarcoma cells. *Int. J. Gynecol. Cancer* 2013; 23(5): 803-8. doi: 10.1097/IGC.0b013e31828c9581.
- 92.** Xiao K, Jiang J, Guan C, Dong C, Wang G, Bai L, Sun J, Hu C and Bai C. Curcumin induces autophagy via activating the AMPK signaling pathway in lung adenocarcinoma cells. *J. Pharmacol. Sci.* 2013; 123(2): 102-109. doi: 10.1254/jphs.13085fp.
- 93.** Jiao D, Wang J, Lu W, Tang X, Chen J, Mou H and Chen Q-Y. Curcumin inhibited HGF-induced EMT and angiogenesis through regulating c-Met dependent PI3K/Akt/mTOR signaling pathways in lung cancer. *Mol. Ther. Oncolytics* 2016; 3: 1-28. doi: 10.1038/mto.2016.18.
- 94.** Pillai GR, Srivastava AS, Hassanein TI, Chauhan DP and Carrier E. Induction of apoptosis in human lung cancer cells by curcumin. *Cancer Lett.* 2004; 208(2): 163-170. doi: 10.1016/j.canlet.2004.01.008.
- 95.** Wu S-H, Hang L-W, Yang J-S, Chen H-Y, Lin H-Y, Chiang J-H, Lu C-C, Yang J-L, Lai T-Y, Ko Y-C and Chung J-G. Curcumin induces apoptosis in human non-small cell lung cancer NCI-H460 cells through ER stress and caspase cascade-and mitochondria-dependent pathways. *Anticancer Res.* 2010; 30(6): 2125-2133. doi: 10.1016/j.canlet.2008.06.031.
- 96.** Tsai M-F, Wang C-C, Chang G-C, Chen C-Y, Chen H-Y, Cheng C-L, Yang Y-P, Wu C-Y, Shih F-Y, Liu C-C, Lin H-P, Jou Y-S, Lin S-C, Lin C-W, Chen W-J, Chan W-K, Chen JJW, Yang P-C. A new tumor suppressor DnaJ-like heat shock protein, HLJ1, and survival of patients with non-small-cell lung carcinoma. *J. Natl. Cancer Inst.* 2006; 98(12): 825-838. doi: 10.1093/jnci/djj229.

- 97.** Zhu JY, Yang X, Chen Y, Jiang Y, Wang SJ, Li Y, Wang X-Q, Meng Y, Zhu M-M, Ma X, Huang C, Wu R, Xie C-F, Li X-T, Geng S-S, Wu J-S, Zhong C-Y and Han H-Y. Curcumin suppresses lung cancer stem cells via inhibiting Wnt/ β -catenin and sonic hedgehog pathways. *Phytother. Res.* 2017; 31(4): 680-688. doi: 10.1002/ptr.5791.
- 98.** Wu H, Zhou J, Zeng C, Wu D, Mu Z, Chen B, Xie Y, Ye Y and Liu J. Curcumin increases exosomal TCF21 thus suppressing exosome-induced lung cancer. *Oncotarget* 2016; 7: 87081-87090. doi: 10.18632/oncotarget.13499.
- 99.** Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, Liu C, Barnes S, Grizzle W, Miller D and Zhang H-G. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. *Mol. Ther.* 2010; 18(9): 1606-1614. doi: 10.1038/mt.2010.105.
- 100.** Heidari S, Mahdiani S, Hashemi M and Kalalinia F. Recent advances in neurogenic and neuroprotective effects of curcumin through the induction of neural stem cells. *Biotechnol. Appl. Biochem.* 2020; 67(3): 430-441. doi: 10.1002/bab.1891.
- 101.** Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, Ko J Y, Lin JT, Lin BR, Ming-Shiang W, Yu HS, Jee SH, Chen GS, Chen TM, Chen CA, Lai MK, Pu YS, Pan MH, Wang YJ, Tsai CC and Hsieh CY. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer. Res.* 2001; 21(4B): 2895-900. doi: 10.1046/j.1365-4362.2002.01372.x.
- 102.** Farzaei MH, Rahimi R and Abdollahi M. The role of dietary polyphenols in the management of inflammatory bowel disease. *Curr. Pharm. Biotechnol.* 2015; 16(3): 196-210. doi: 10.2174/1389201016666150118131704.
- 103.** Gramza A, Korczak J and Amarowicz R. Tea polyphenols-their antioxidant properties and biological activity-a review. *Pol. J. Food Nutr. Sci.* 2005; 14(55): 219-235.
- 104.** Feng WY. Metabolism of green tea catechins: an overview. *Curr. Drug. Metab.* 2006; 7(7): 755-809. doi: 10.2174/138920006778520552.
- 105.** Musial C, Kuban-Jankowska A and Gorska-Ponikowska M. Beneficial properties of green tea catechins. *Int. J. Mol. Sci.* 2020; 21(5): 1744-1755. doi: 10.3390/ijms21051744.
- 106.** Li Q, Kakizaki M, Kuriyama S, Sone T, Yan H, Nakaya N, Mastuda-Ohmori K and Tsuji I. Green tea consumption and lung cancer risk: the Ohsaki study. *Br. J. Cancer* 2008; 99: 1179-1184. doi: 10.1038/sj.bjc.6604645.
- 107.** Fritz H, Seely D, Kennedy DA, Fernandes R, Cooley K and Fergusson D. Green tea and lung cancer: a systematic review. *Integr. Cancer Ther.* 2013; 12(1): 7-24. doi: 10.1177/1534735412442378.
- 108.** Tang N, Wu Y, Zhou B, Wang B and Yu R. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. *Lung Cancer* 2009; 65(3): 274-283. doi: 10.1016/j.lungcan.2008.12.002.
- 109.** Zhong Z, Dong Z, Yang L, Chen X and Gong Z. Inhibition of proliferation of human lung cancer cells by green tea catechins is mediated by upregulation of let-7. *Exp. Ther. Med.* 2012; 4: 267-272. doi: 10.3892/etm.2012.580.
- 110.** Lu Q-Y, Jin Y, Mao JT, Zhang Z-F, Heber D, Dubinett SM and Rao J. Green tea inhibits cyclooxygenase-2 in non-small cell lung cancer cells through the induction of Annexin-1. *Biochem. Biophys. Res. Commun.* 2012; 427: 725-730. doi: 10.1016/j.bbrc.2012.09.125.
- 111.** Lee JM, Yanagawa J, Peebles KA, Sharma S, Mao JT and Dubinett SM.

- Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Crit. Rev. Oncol. Hematol.* 2008; 66(3): 208-217. doi: 10.1016/j.critrevonc.2008.01.004.
- 112.** Milligan SA, Burke P, Coleman DT, Bigelow RL, Steffan JJ, Carroll JL Williams BJ and Cardelli JA. The green tea polyphenol EGCG potentiates the Antiproliferative activity of c-met and epidermal growth factor receptor inhibitors in non-small cell lung cancer cells. *Clin. Cancer Res.* 2009; 15(15): 4885-4894. doi: 10.1158/1078-0432.CCR-09-0109.
- 113.** Sadava D, Whitlock E and Kane SE. The green tea polyphenol, epigallocatechin-3-gallate inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells. *Biochem. Biophys. Res. Commun.* 2007; 360(1): 233-237. doi: 10.1016/j.bbrc.2007.06.030.
- 114.** Zhou H, Chen JX, Yang CS, Yang MQ, Deng Y and Wang H. Gene regulation mediated by microRNAs in response to green tea polyphenol EGCG in mouse lung cancer. *BMC Genom.* 2014; 15: 1-10. doi: 10.1186/1471-2164-15-S11-S3.
- 115.** Schönthal AH. Adverse effects of concentrated green tea extracts. *Mol. Nutr. Food Res.* 2011; 55(6): 874-885. doi: 10.1002/mnfr.201000644.
- 116.** Hagi A, Azimi HandRahimi R. A comprehensive review on pharmacotherapeutics of three phytochemicals, curcumin, quercetin, and allicin, in the treatment of gastric cancer. *J. Gastrointest. Cancer* 2017; 48: 314-320. doi: 10.1007/s12029-017-9997-7.
- 117.** Bahramsoltani R, Farzaei MH, Farahani MS and Rahimi R. Phytochemical constituents as future antidepressants: a comprehensive review. *Rev. Neurosci.* 2015; 26(6): 699-719. doi: 10.1515/revneuro-2015-0009.
- 118.** Khazeei Tabari MA, Iranpanah A, Bahramsoltani RandRahimi R. Flavonoids as promising antiviral agents against SARS-CoV-2 infection: A mechanistic review. *Molecules* 2021; 26(13): 1-36. doi: 10.3390/molecules26133900.
- 119.** Wu L, Li J, Liu T, Li S, Feng J, Yu Q, Zhang J, Chen J, Zhou Y, Ji J, Chen K, Mao Y, Wang F, Dai W, Fan X, Wu J and Guo C. Quercetin shows anti-tumor effect in hepatocellular carcinoma LM3 cells by abrogating JAK2/STAT3 signaling pathway. *Cancer Med.* 2019; 8(10): 4806-4820. doi: 10.1002/cam4.2388.
- 120.** Yang J-H, Hsia T-C, Kuo H-M, Chao P-DL, Chou C-C, Wei Y-H and Chung J-G. Inhibition of lung cancer cell growth by quercetin glucuronides via G2/M arrest and induction of apoptosis. *Drug Metab. Dispos.* 2006; 34(2): 296-304. doi: 10.1124/dmd.105.005280.
- 121.** Balakrishnan S, Bhat F, Raja Singh P, Mukherjee S, Elumalai P, Das S, Patra CR and Arunakaran J. Gold nanoparticle-conjugated quercetin inhibits epithelial-mesenchymal transition, angiogenesis and invasiveness via EGFR/VEGFR-2-mediated pathway in breast cancer. *Cell Prolif.* 2016; 49: 678-697. doi: 10.1111/cpr.12296.
- 122.** Pradhan SJ, Mishra R, Sharma P and Kundu GC. Quercetin and sulforaphane in combination suppress the progression of melanoma through the down-regulation of matrix metalloproteinase-9. *Exp. Ther. Med.* 2010; 1: 915-920. doi: 10.3892/etm.2010.144.
- 123.** Yang J and Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev. Cell* 2008; 14(6): 818-829. doi: 10.1016/j.devcel.2008.05.009.

- 124.** Chang J-H, Lai S-L, Chen W-S, Hung W-Y, Chow J-M, Hsiao M, Lee W-J and Chien M-H. Quercetin suppresses the metastatic ability of lung cancer through inhibiting Snail-dependent Akt activation and Snail-independent ADAM9 expression pathways. *Biochim. Biophys. Acta. Mol. Cell. Res.* 2017; 1864(10): 1746-1758. doi: 10.1016/j.bbamcr.2017.06.017.
- 125.** Xingyu Z, Peijie M, Dan P, Youg W, Daojun W, Xinzheng C and Xijun Z. Quercetin suppresses lung cancer growth by targeting Aurora B kinase. *Cancer Med.* 2016; 5(11): 3156-3165. doi: 10.1002/cam4.891.
- 126.** Mukherjee A and Khuda-Bukhsh AR. Quercetin down-regulates IL-6/STAT-3 signals to induce mitochondrial-mediated apoptosis in a non-small-cell lung-cancer cell line, A549. *J. Pharmacopuncture* 2015; 18(1): 19-26. doi: 10.3831/KPI.2015.18.002.
- 127.** Klimaszewska-Wiśniewska A, Hałas-Wiśniewska M, Izdebska M, Gagat M, Grzanka A and Grzanka D. Antiproliferative and antimetastatic action of quercetin on A549 non-small cell lung cancer cells through its effect on the cytoskeleton. *Acta Histochem.* 2017; 119(2): 99-112. doi: 10.1016/j.acthis.2016.11.003.
- 128.** Chakraborty S, Stalin S, Das N, Choudhury ST, Ghosh S and Swarnakar S. The use of nano-quercetin to arrest mitochondrial damage and MMP-9 upregulation during prevention of gastric inflammation induced by ethanol in rat. *Biomaterials* 2012; 33(10): 2991-3001. doi: 10.1016/j.biomaterials.2011.12.037.
- 129.** Zheng K, Zhang G, Jiang N, Yang S, Li C, Meng Z, Guo Q and Long G. Analysis of the transcriptome of *Marsdenia tenacissima* discovers putative polyoxypregnane glycoside biosynthetic genes and genetic markers. *Genomics* 2014; 104(3): 186-193. doi: 10.1016/j.ygeno.2014.07.013.
- 130.** Ye B, Li J, Li Z, Yang J, Niu T and Wang S. Anti-tumor activity and relative mechanism of ethanolic extract of *Marsdenia tenacissima* (Asclepiadaceae) against human hematologic neoplasm in vitro and in vivo. *J. Ethnopharmacol.* 2014; 153(1): 258-267. doi: 10.1016/j.jep.2014.02.035.
- 131.** Wang XL, Li QF, Yu KB, Peng SL, Zhou Y and Ding LS. Four new pregnane glycosides from the stems of *Marsdenia tenacissima*. *Helv. Chim. Acta* 2006; 89(11): 2738-2744. doi: 10.1080/1028602031000135549.
- 132.** Huang Z, Wang Y, Chen J, Wang R and Chen Q. Effect of Xiaoaiping injection on advanced hepatocellular carcinoma in patients. *J. Tradit. Chin. Med.* 2013; 33(1): 34-38. doi: 10.1016/s0254-6272(13)60097-7.
- 133.** Zhu R-J, Shen X-L, Dai L-L, Ai X-Y, Tian R-H, Tang R and Hu Y-J. Total aglycones from *Marsdenia tenacissima* increases antitumor efficacy of Paclitaxel in nude mice. *Molecules* 2014; 19(9): 13965-13975. doi: 10.3390/molecules190913965.
- 134.** Wang X, Yan Y, Chen X, Zeng S, Qian L, Ren X, Wei J, Yang X, Zhou Y, Gong Z and Xu Z. The antitumor activities of *Marsdenia tenacissima*. *Front Oncol.* 2018; 8: 473-499. doi: 10.3389/fonc.2018.00473.
- 135.** Yao S, To KK-W, Wang Y-Z, Yin C, Tang C, Chai S, Ke C-Q, Lin G and Ye Y. Polyoxypregnane steroids from the stems of *Marsdenia tenacissima*. *J. Nat. Prod* 2014; 77(9): 2044-2053. doi: 10.1021/np500385b.
- 136.** Pang X, Kang L-P, Yu H-S, Zhao Y, Han L-F, Zhang J, Xiong C-Q, Zhang L-X, Yu L-Y and Ma B-P. New polyoxypregnane glycosides from the roots of *Marsdenia tenacissima*. *Steroids* 2015; 93: 68-76. doi: 10.1016/j.steroids.2014.11.004.
- 137.** Huang Z, Lin H, Wang Y, Cao Z, Lin W and Chen Q. Studies on the anti-angiogenic

- effect of *Marsdenia tenacissima* extract in vitro and in vivo. *Oncol. Lett.* 2013; 5: 917-922. doi: 10.3892/ol.2013.1105.
- 138.** Bing-Yu C, Dong C, Jian-Xin L, Kai-Qiang L, Meng-Meng J, Jing-Jing Z, Xu-Jun H, Ke H, Hou-Quan T, Xiao-Zhou M, You-Min Y, Wei Z, Meng-Hua Z and Zhen W. *Marsdeniae tenacissimae* extract (MTE) suppresses cell proliferation by attenuating VEGF/VEGFR2 interactions and promotes apoptosis through regulating PKC pathway in human umbilical vein endothelial cells. *Chin. J. Nat. Med.* 2016; 14(12): 922-930. doi: 10.1016/S1875-5364(17)30017-1.
- 139.** Wei F, Li S, Jing-Qian Z, Cang Z, Song Q, Ying T, Yang L, Sen-Sen L and Sheng-Tao Y. *Marsdenia tenacissima* extract induces G0/G1 cell cycle arrest in human esophageal carcinoma cells by inhibiting mitogen-activated protein kinase (MAPK) signaling pathway. *Chin. J. Nat. Med.* 2015; 13(6): 428-437. doi: 10.1016/S1875-5364(15)30036-4.
- 140.** Wang Z, Qi F, Cui Y, Zhao L, Sun X, Tang W and Cai P. An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. *Biosci. Trends* 2018; 12(3): 220-239. doi: 10.5582/bst.2018.01144.
- 141.** Hu Y, Liu P, Kang L, Li J, Li R and Liu T. Mechanism of *Marsdenia tenacissima* extract promoting apoptosis of lung cancer by regulating Ca²⁺/CaM/CaMK signaling. *J. Ethnopharmacol.* 2020; 251: 1-10. doi: 10.1016/j.jep.2019.112535.
- 142.** Zhao C, Hao H, Zhao H, Ren W, Jiao Y, An G, Sun H, Han S and Li P. *Marsdenia tenacissima* extract promotes gefitinib accumulation in tumor tissues of lung cancer xenograft mice via inhibiting ABCG2 activity. *J. Ethnopharmacol* 2020; 255: 1-15. doi: 10.1016/j.jep.2020.112770.
- 143.** Blackhall F, Ranson M and Thatcher N. Where next for gefitinib in patients with lung cancer? *Lancet Oncol.* 2006; 7(6): 499-507. doi: 10.1016/S1470-2045(06)70725-2.
- 144.** McKillop D, McCormick AD, Millar A, Miles GS, Phillips PJ and Hutchison M. Cytochrome P450-dependent metabolism of gefitinib. *Xenobiotica* 2005; 35(1): 39-50. doi: 10.1080/00498250400026464.
- 145.** Jiao Y-N, Wu L-N, Xue D, Liu X-J, Tian Z-H, Jiang S-T and Han S-Y. *Marsdenia tenacissima* extract induces apoptosis and suppresses autophagy through ERK activation in lung cancer cells. *Cancer Cell Int.* 2018; 18: 1-12. doi: 10.1002/mnfr.201600437.
- 146.** Hao K, Chen BY, Li KQ, Zhang Y, Li CX, Wang Y, Jiang L-X, Shen J, Guo X-c, Zhang W, Zhu M-h and Wang Z. Cytotoxicity of anti-tumor herbal *Marsdeniae tenacissimae* extract on erythrocytes. *J. Zhejiang Univ. Sci. B* 2017; 18: 597-604. doi: 10.1631/jzus.B1600228.
- 147.** Wu L, Guo L, Liang Y, Liu X, Jiang L and Wang L. Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway. *Oncol. Rep.* 2015; 34: 3311-3317. doi: 10.3892/or.2015.4279.
- 148.** Gao L, Shao T, Zheng W and Ding J. Curcumin suppresses tumor growth of gemcitabine-resistant non-small cell lung cancer by regulating lncRNA-MEG3 and PTEN signaling. *Clin. Transl. Oncol.* 2021; 23(7): 1386-1393. doi: 10.1007/s12094-020-02531-3.
- 149.** Xu X and Zhu Y. Curcumin inhibits human non-small cell lung cancer xenografts by targeting STAT3 pathway. *Am. J. Transl. Res.* 2017; 9(8): 3633-3641. doi: 10.1080/00498250400026464.
- 150.** Wang H, Bian S and Yang CS. Green tea polyphenol EGCG suppresses lung cancer cell

growth through upregulating miR-210 expression caused by stabilizing HIF-1 α . *Carcinogenesis* 2011; 32(12): 1881-1889. doi: 10.1093/carcin/bgr218.

151. Lu QY, Yang Y, Jin YS, Zhang ZF, Heber D, Li FP, Dubinett SM, Sondej MA, Loo JA and Rao JY. Effects of green tea extract on lung cancer A549 cells: proteomic identification of proteins associated with cell migration. *Proteomics* 2009; 9(3): 757-767. doi: 10.1002/pmic.200800019.

152. Youn HS, Jeong J-C, Jeong YS, Kim E-J and Um S-J. Quercetin potentiates apoptosis by inhibiting nuclear factor-kappaB signaling in H460 lung cancer cells. *Biol. Pharm. Bull.* 2013; 36(6): 944-951. doi: 10.1248/bpb.b12-01004.

153. Zheng S-Y, Li Y, Jiang D, Zhao J and Ge J-F. Anticancer effect and apoptosis induction by quercetin in the human lung cancer cell line A-549. *Mol. Med. Rep.* 2011; 5: 822-826. doi: 10.3892/mmr.2011.726.

154. Dong Y, Yang Y, Wei Y, Gao Y, Jiang W, Wang G and Wang D. Facile synthetic nano-curcumin encapsulated Bio-fabricated nanoparticles induces ROS-mediated apoptosis and migration blocking of human lung cancer cells. *Process Biochem.* 2020; 95: 91-98. doi: 10.1016/j.procbio.2020.05.011.

155. Khan MN, Haggag YA, Lane ME, McCarron PA and Tambuwala MM. Polymeric nano-encapsulation of curcumin enhances its

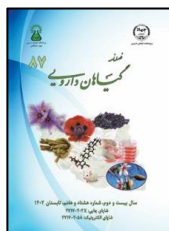
anti-cancer activity in breast (MDA-MB231) and lung (A549) cancer cells through reduction in expression of HIF-1 α and nuclear p65 (REL A). *Curr. Drug Deliv.* 2018; 15(2): 286-295. doi: 10.2174/1567201814666171019104002.

156. Ibrahim S, Tagami T, Kishi T and Ozeki T. Curcumin marinosomes as promising nano-drug delivery system for lung cancer. *Int. J. Pharm.* 2018; 540(1-2): 40-49. doi: 10.1016/j.ijpharm.2018.01.051.

157. Chen B-H, Hsieh C-H, Tsai S-Y, Wang C-Y and Wang C-C. Anticancer effects of epigallocatechin-3-gallate nanoemulsion on lung cancer cells through the activation of AMP-activated protein kinase signaling pathway. *Sci. Rep.* 2020; 10: 1-11. doi: 10.1038/s41598-020-62136-2.

158. Sun B, Hu N, Han L, Pi Y, Gao Y and Chen K. Anticancer activity of green synthesised gold nanoparticles from *Marsdenia tenacissima* inhibits A549 cell proliferation through the apoptotic pathway. *Artif. Cells Nanomed. Biotechnol.* 2019; 47(1): 4012-4019. doi: 10.1080/21691401.2019.1575844.

How to cite this article: Malakootikhah J, Yahyaei M, Ghafarzadegan R, Ghafarzadegan R. Herbal nano-formulations in lung cancer: Superiorities to original forms. *Journal of Medicinal Plants* 2023; 22(87): 1-25.
doi:



فصلنامه گیاهان دارویی

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مقاله مروری

نانو فرمول‌های گیاهی در سرطان ریه: برتری‌ها نسبت به اشکال خالص جواد ملکوتی خواه^{۱*}، محمد یحیائی^۲، رضا غفارزادگان^۳، رضوان غفارزادگان^۴

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اطلاعات مقاله	چکیده
گل‌واژگان:	مقدمه: سرطان ریه (LC) شایع‌ترین نوع سرطان است و میزان مرگ و میر و عوارض آن در سراسر جهان رو به افزایش است. علی‌رغم اینکه پرتودرمانی، شیمی‌درمانی و روش‌های جراحی از جمله راهبردهای درمانی رایج در برابر LC هستند، با این وجود این روش‌ها اثربخشی کافی ندارند و ممکن است استفاده از آنها با اثرات نامطلوبی همراه باشد. در نتیجه شناسایی راه‌های جایگزین برای درمان و کنترل بیماران LC ضروری است. هدف: در این مطالعه مروری، هدف بررسی تأثیرات درمانی داروهای گیاهی مبتنی بر نانو (کورکومین، چای سبز، کورستین و مارسدنیا تناسیسیما) و مقایسه آنها با تمرکز بر جنبه‌های مکانیکی آنها در برابر LC بود. روش بررسی: پایگاه‌های اطلاعاتی Google Scholar، Web of Science، PubMed، Scopus و SID به طور سیستماتیک و بدون هیچ گونه محدودیتی برای زبان و زمان مورد جستجو قرار گرفتند. نتایج: نتایج ارزیابی نشان داد که این فرآورده‌های گیاهی از طریق مکانیسم‌های مختلفی مانند تنظیم سیستم ایمنی، تحریک آپوپتوز سلولی و اتوفاژی می‌توانند در درمان LC مفید باشند. با این حال، استفاده همزمان از داروهای گیاهی و فرمول‌های نانو (نانوذرات اکسیدروی، نقاط کوانتومی کادمیوم سولفید، نانوذرات کونژوگه با طلا می‌تواند به طور چشمگیری بر برخی از محدودیت‌های طب گیاهی غلبه کند و کارایی آن را در برابر LC افزایش دهد. نتیجه‌گیری: به نظر می‌رسد استفاده از نانو فرمولاسیون‌ها و داروهای گیاهی باعث بهبود LC می‌شود. با این حال، مطالعات بیشتری با حجم نمونه بزرگ برای اثبات این یافته‌ها مورد نیاز است.
گیاه دارویی	
سرطان ریه	
کورکومین	
کورستین	
چای سبز	
<i>Marsdenia tenacissima</i>	

مخفف‌ها: LC، سرطان ریه؛ NPs، نانوذرات؛ CdS QDs، نقاط کوانتومی کادمیوم سولفید؛ AuNPs، نانوذرات طلا

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تاریخ دریافت: ۱ مرداد ۱۴۰۲؛ تاریخ دریافت اصلاحات: ۳ آبان ۱۴۰۲؛ تاریخ پذیرش: ۱۴ آبان ۱۴۰۲

doi:

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