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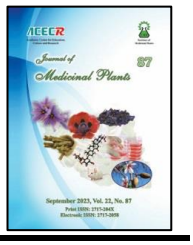

Review Article

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

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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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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

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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-κB), 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)-1β, 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

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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 (ERα) and Estrogen receptor beta (Erβ), have been identified in LC patients. The existence of Erα has been approved in the cell lines of NSCLC, whereas Erβ overexpression has a prognosticating role in this type of LC [44].

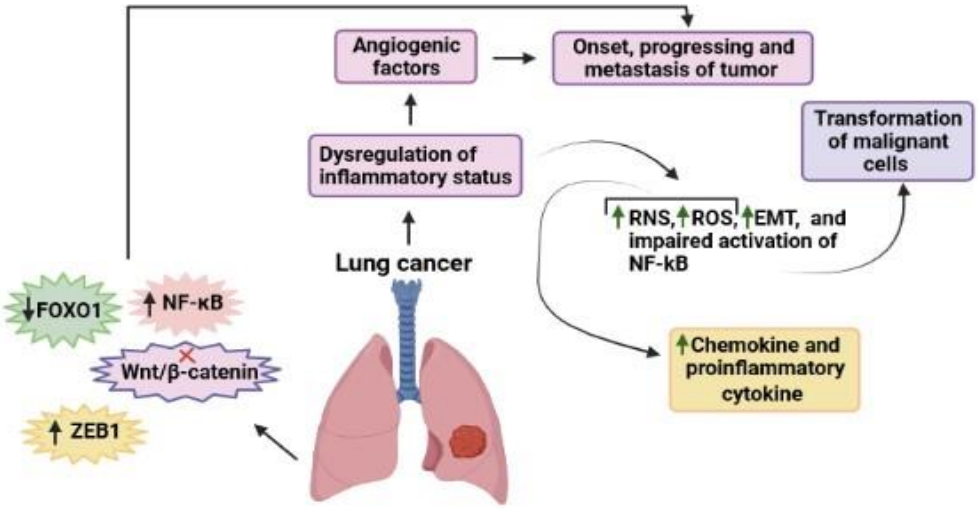

Fig. 1. Pathogenesis of lung cancer**.** NF-κB, Nuclear factor-kappa B; FOXO1, Forkhead Box O1; ZEB1, Zinc Finger E-Box Binding Homeobox 1; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; EMT, Epithelial-to-mesenchymal transformation.

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

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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-κB 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 Nd_2O_3) 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

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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-κB, 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-

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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 (ALDHA1), 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].

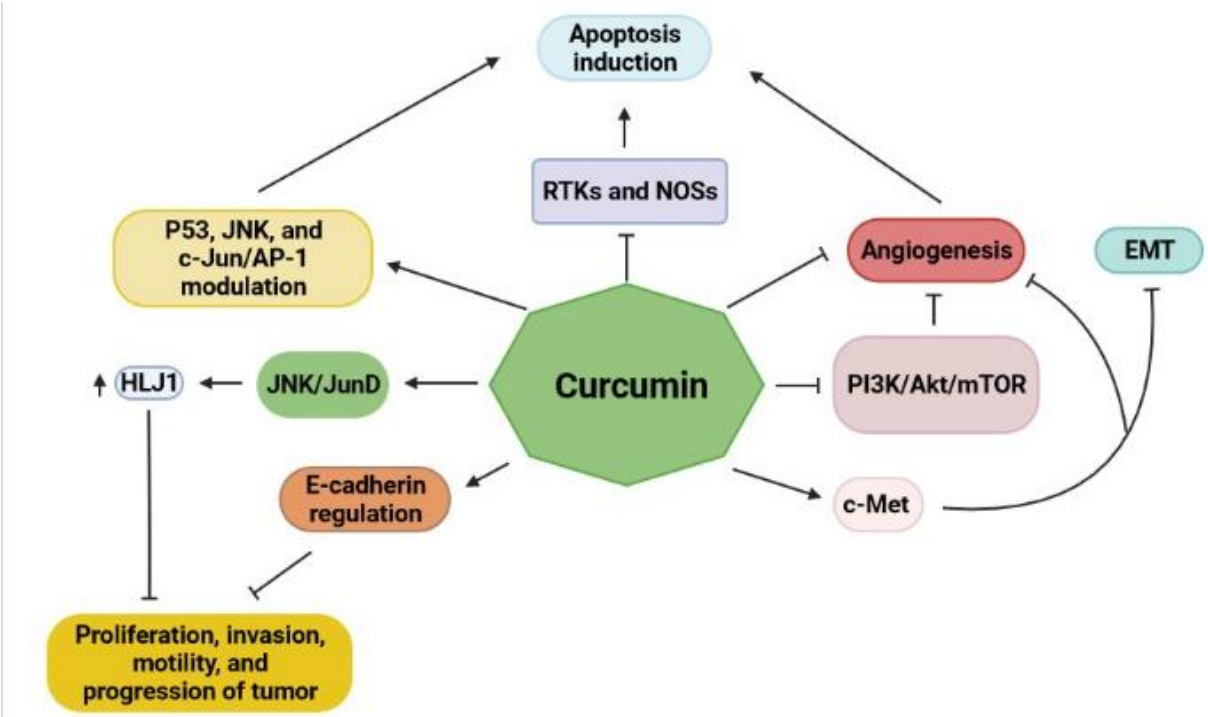

Fig. 2. Mechanism of action of *curcumin* against lung cancer. C-Met, Mesenchymal epithelial transition factor; EMT, Epithelial-to-mesenchymal transformation; RTKs, Receptor tyrosine kinases; NOSs, Nitric oxide synthases; and HLJ1, DnaJ-like heat shock protein.

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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 E_2 (PGE_2) and the expression of Cyclooxygenase-2 (COX-2). Elevated COX-2 expression has been demonstrated in NSCLC; furthermore, COX-2 increases PGE_2 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].

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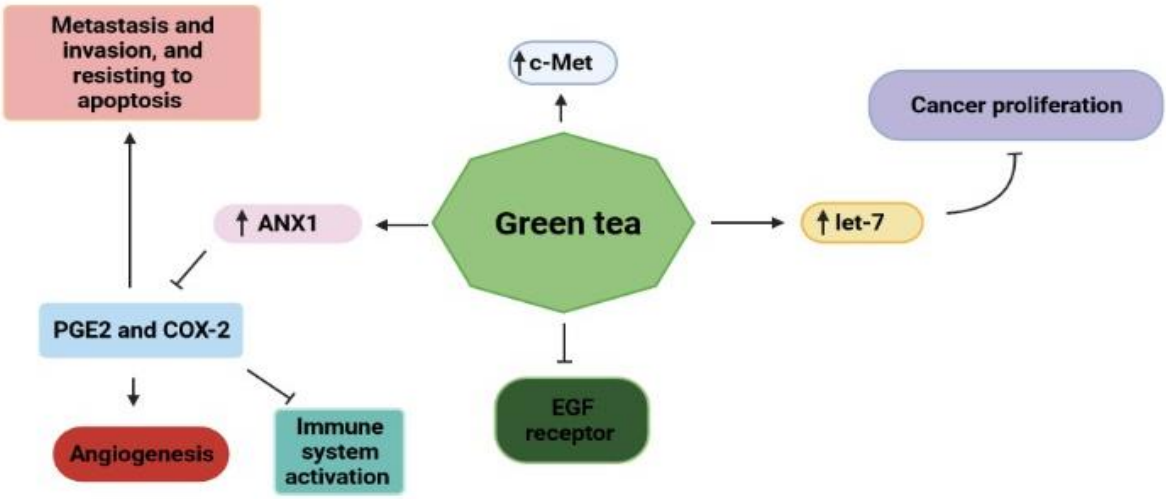

Fig. 3. Mechanism of action of green tea against lung cancer**.** C-Met, Mesenchymal epithelial transition factor; Let-7, lethal-7; ANX1, Annexin A1; PGE2, Prostaglandin E2; and COX-2, Cyclooxygenase-2.

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-kB, 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-κB, 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.

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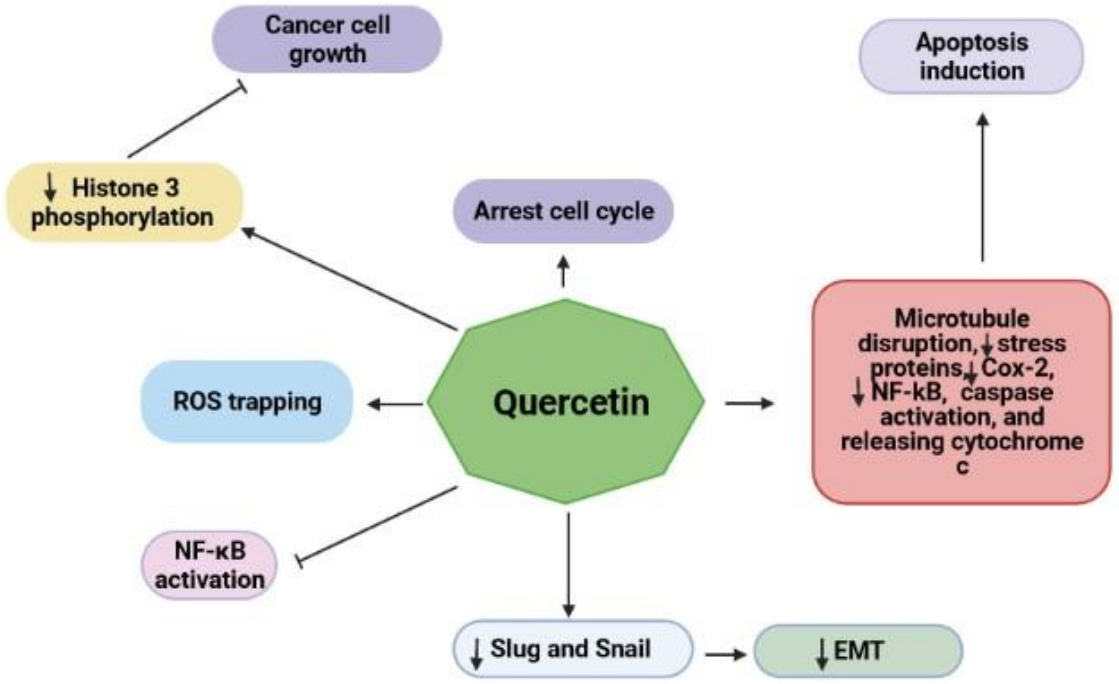

Fig. 4. Mechanism of action of *quercetin* against lung cancer. EMT, Epithelial-to-mesenchymal transformation; NF-κB, Nuclear factor kappa B; ROS, Reactive oxygen species; and COX-2, Cyclooxygenase-2.

***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

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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.

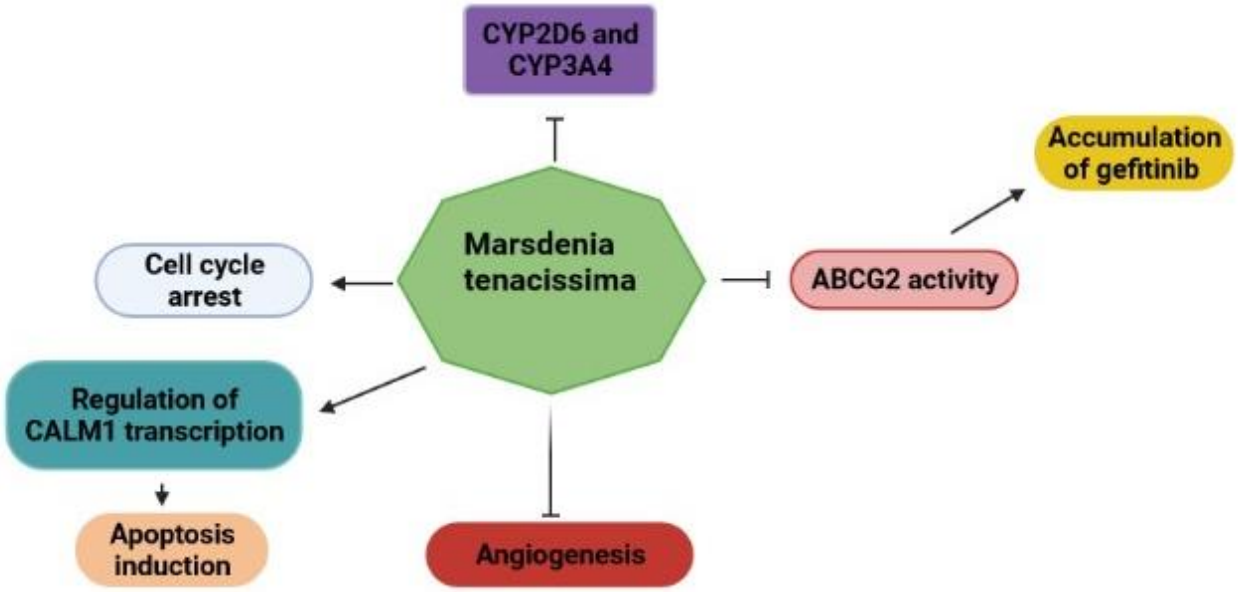

Fig. 5. Mechanism of action of *Marsdenia tenacissima* against lung cancer. ABCG2, ATP Binding Cassette Subfamily G Member 2; CALM1, Calmodulin 1; CYP2D6, Cytochrome P450 2D6; CYP3A4, Cytochrome P450 3A4.

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

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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 μM	Apoptosis induction and cell migration inhibition	in vitro	[154]
Cur-PLGA-NPs	10, 20, and 30 μM	Inhibition of colony formation and cell migration	in vitro	[155]
CURM	0-12.5 μg/ml	Cell proliferation inhibition and increase of antioxidant activity	in vitro	[156]
Nano-EGCG	0-10 μM	Cell growth inhibition and colony formation suppression	in vitro	[157]
CdS QDs of tea	10, 25, and 50μg/mL	Apoptosis induction and cell growth inhibition	in vitro	[57]
Cet-QUE NPs	0-32 μg/mL	Apoptosis induction and cell growth inhibition	in vitro/in vivo	[58]
QUR-M	0-32 μg/mL	Apoptosis induction and cell proliferation inhibition	in vitro	[59]
AuNPs from M. tenacissima	2.5- 25 μg/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-κB, 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.

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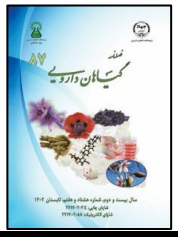

مقاله مروری

نانو فرمول‌های گیاهی در سرطان ریه: برتری‌ها نسبت به اشکال خالص

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Marsdenia tenacissima

چکیده

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 راه های 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 موردنیاز است.

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

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