Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/75/2024.LA19342

Potential and Challenges of Terpenoids in Cancer Therapy: Mechanistic Review and Future Perspectives

Houlin He

School of Chemical Engineering, Xiangtan University, Xiangtan, China

hehoulin080690@gmail.com

Abstract. Terpenoids have shown promising therapeutic effects in a variety of cancer models due to their multi-targeted anticancer mechanisms, modulation of the tumor microenvironment, and enhancement of the immune response. However, terpenoids face many challenges in clinical applications, mainly including their complex chemical structures, low bioavailability, and poor targeting. These factors limit their stability and anticancer effects in vivo. This paper reviews the anticancer mechanisms of terpenoids, the challenges of clinical applications, and the corresponding strategies to address them. Future studies should improve these deficiencies through chemical modification and nanotechnology to enhance drug performance and promote their clinical applications.

Keywords: Terpenoids, Tumor microenvironment, Bioavailability, Targeting, Anti-cancer mechanism.

1. Introduction

Cancer, the second leading cause of death globally, poses a significant threat to human life and safety. Despite advances in treatment, there is still no completely effective cure. In 2020, 19.3 million cancer cases and 10 million cancer-related deaths were reported worldwide, with breast cancer in women, colorectal cancer, and lung cancer being the three most common types. It is projected that by 2040, cancer incidence will rise by 47% compared to 2020 [1]. While five-year survival rates have improved in recent years, the prognosis for certain malignant tumors remains poor. Currently, a range of therapeutic approaches are employed in cancer treatment, with chemotherapy remaining a cornerstone. Chemotherapeutic drugs act through various mechanisms. Beyond inducing apoptosis and inhibiting cancer cell proliferation, some drugs can alter the tumor microenvironment or be used in combination with other therapies to enhance the sensitivity of cancer cells to treatment and overcome drug resistance. In some cases, chemotherapy is combined with other therapies, such as immunotherapy or differentiation therapy, to boost efficacy. As a result, the search for and development of new chemotherapeutic agents continues to be a priority.

Terpenoids, a large and diverse class of compounds, exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, antiviral, and anticancer properties. The anticancer mechanisms of terpenoids are multifaceted and often involve multiple therapeutic targets. Terpenoids are abundant in natural products, and some of the foods we commonly consume, such as lemons and carrots, are rich in these compounds. Diets high in terpenoids have been linked to cancer prevention. However, despite their promising anticancer potential, the clinical use of terpenoids is

DOI: 10.54254/2753-8818/75/2024.LA19342

limited due to their generally low toxicity, poor selectivity, and low bioavailability [2]. Moreover, because terpenoids are primarily derived from natural sources, challenges in synthesis and extraction further hinder their large-scale production. This research aims to explore the anticancer mechanisms of several terpenoids, while also proposing the challenges they face and potential solutions for overcoming these obstacles.

2. Mechanisms of anticancer effects of terpenoids

2.1. Multi-targeted effects of terpenoids

Terpenoids usually act on multiple targets to exert anticancer effects, for example, the monoterpene thymol damages mitochondrial membranes by altering intracellular reactive oxygen species (ROS) levels, activating caspase 9 and caspase 3, and initiating the endogenous apoptotic pathway to promote apoptosis in cancer cells. At the same time, thymol can stop cell division at G0 phase and inhibit the proliferation of cancer cells [1]. Terpenoids can induce cell cycle arrest and prevent cancer cell division. Some terpenoids, such as diterpenoids, can further inhibit tumor growth by inhibiting abnormally activated proliferative signaling pathways in cancer cells, further inhibiting tumor growth. Promoting apoptosis and inhibiting proliferation of cancer cells is a conventional method of chemotherapy in the fight against cancer,and there are a large number of terpenoids that can fight cancer in this way.

The tumor microenvironment (TME) is a complex ecosystem composed of tumor cells, immune cells, stromal cells, blood vessels and extracellular matrix. Terpenoids enhance the immune response by modulating different components of the tumor microenvironment, inhibiting angiogenesis around tumor cells or activating immune cells to limit tumor growth and metastasis. Terpenoids can also be used in combination with other anticancer drugs to enhance the sensitivity of cancer cells to chemotherapeutic drugs while reducing the toxicity of chemotherapeutic drugs. For example, curcumin can reduce the nephrotoxicity of cisplatin and enhance the killing effect of cisplatin on cancer cells when used in combination with cisplatin (CDDP). Terpenoids have therapeutic effects on a wide range of cancers, but the efficacy of terpenoids in different cancers varies due to the different biological properties of each cancer. Diterpenoids such as paclitaxel are effective in breast, lung and ovarian cancers, prolonging patient survival, and are particularly effective in ovarian cancer. Curcumin can increase the sensitivity of rectal, pancreatic and prostate cancers to drugs [2].

2.2. Mechanisms of anticancer effects of representative Thessalonian compounds

Atractylenolides are a class of sesquiterpene lactones, and Atractylenolide I (ATT-I) fights cancer by enhancing antigen presentation to tumor cells. Atractylenolide I enhances T-cell cytotoxicity by targeting the 26S subunit of the proteasome, non-ATPase 4 (PSMD4), which promotes the presentation of tumor antigens, increasing the immune system's ability to kill cancer cells and improving the tumor's response to immunotherapy. Similarly, ATT-I can be combined with immune checkpoint PD-1 inhibitors to significantly improve the therapeutic effect [3]. Astragaloside is a class of triterpenoid compounds, mostly found in traditional Chinese medicine. It can be used as a chemopreventive agent for tumors due to its cheap, non-toxic, and orally consumable properties, and has preventive effects against viral hepatitis B and intestinal fibrotic lesions [4]. Astragaloside II and IV, the main components of astragaloside, have multiple anticancer mechanisms, in addition to promoting apoptosis of cancer cells, inhibiting the proliferation of cancer cells, and changing the microenvironment of tumors. It can also reverse the drug resistance of cancer cells. Astragaloside IV in A549 and H1299 cancer cells destroys the drug resistance of tumor cells by regulating the expression of corresponding proteins, enzymes and Beclin factors [5]. Carotenoids are a group of tetraterpenoids that enter the human body and are converted to vitamin A. Vitamin A has multiple anticancer activities, and retinol is a form of vitamin A. Retinol is used in the endoplasmic reticulum. The endoplasmic reticulum of retinol should be used to induce autophagy in cancer cells to fight cancer. In addition, fenretinide (4-HPR), a derivative of vitamin A, has the ability to induce differentiation of cancer cells, albeit poorly, but in combination with retinoic acid RA, it can exert a greater ability to induce differentiation [6].

DOI: 10.54254/2753-8818/75/2024.LA19342

In summary, terpenoids have a wide range of targets and diverse anticancer mechanisms, and can either kill or inhibit the growth of cancer cells through traditional exogenous drug action, or act as sensitizers to increase the responsiveness of cancer cells to treatment. In addition, terpenoids have the potential to control cancer by inducing differentiation of cancer cells. Thus, terpenoids have great potential for anticancer drug development, but their clinical application still faces many challenges.

3. Limitations of terpenoids in clinical applications

3.1. Structural Complexity

Terpenoids possess complex carbon skeletons and functional groups and also involve stereochemical ring structures. With the addition of the carbon-penta-isoprene unit (C5H8), the length of the carbon chain grows and the difficulty of synthesis increases. For example, the linear terpene farnesol is simpler to synthesize, whereas the polycyclic terpene paclitaxel cannot be obtained synthetically. In addition, terpenoids have multiple chiral centers, and these stereostructures have a significant impact on drug activity, making the precise synthesis of terpenoids with specific stereostructures a great challenge. The conformational relationship of chemical drugs is a major focus of drug research, and the efficacy of terpenoids often depends on these complex structures, including chirality, positional relationship between functional groups, carbon chain length, etc., which affect the toxicity, aqueous solubility, bioavailability and other pharmacokinetic properties of the drugs.

3.2. Bioavailability and pharmacokinetics problems

Terpenoids are usually hydrophobic with high lipid solubility, which limits their absorption and metabolism in the body, making them inefficient in passing through epithelial cell membranes, and are usually degraded by metabolic enzymes in the intestinal tract or excreted by exocytosis proteins, decreasing absorption and bioavailability. In addition, due to their hydrophobicity, terpenoids have a short circulation time in the body and are easily and rapidly cleared, affecting their efficacy. For example, paclitaxel is a class of diterpenoids with poor water solubility and rapid metabolism, which greatly limits its clinical applications [6]. The metabolic stability and absorption of terpenoids is also a major challenge. Terpenoids usually contain unsaturated bonds, cyclic structures, and various functional groups, and are susceptible to oxidative metabolism by metabolizing enzymes, especially the hepatic CYP450 enzyme system. For example, monoterpenes and sesquiterpenes are often metabolized and inactivated in the liver due to their small molecular weight and abundance of double bonds. Geraniol, a common monoterpene, is susceptible to oxidation in vivo to form geranic acid, which affects its activity and metabolism.

3.3. Poor targeting and selectivity

The presence of off-target effects of terpenoids in anticancer therapy refers to the fact that these compounds affect not only cancer cells but also other normal cells and tissues, resulting in toxicity or side effects. This phenomenon is often observed in clinical practice, especially when terpenoids are not sufficiently targeted or selective. Resveratrol is a naturally occurring polyphenolic terpenoid with antioxidant and anticancer activity. However, resveratrol produces off-target effects that interfere with normal cellular metabolic pathways and may also induce apoptosis or inhibit cell proliferation, negatively affecting normal cells. In addition, resveratrol may have toxic effects on the liver and kidney at high concentrations [7]. Terpenoids generally have low toxicity, but may be toxic to normal cells at higher drug concentrations. This toxicity due to low selectivity needs to be addressed by chemical modification and structural optimization to improve their safety and efficacy.

DOI: 10.54254/2753-8818/75/2024.LA19342

4. Strategies to enhance the anticancer activity of terpenoids

4.1. Chemical modification and structure optimization

By chemically modifying the structure of terpenoids, their anticancer activity and targeting properties can be significantly improved. Tong et al. found that the modification of the chemical structure on the A-ring and C-17 side chain could significantly change the biological activity of PDD through the structural modification of PDD-type ginsenosides, proving that the chemical modification had a significant effect on the drug activity [8]. Chemical modifications can also improve the water solubility and bioavailability of terpenoids. For example, the methylenecyclopentanone (enone) in the D-ring of the tetracyclic diterpenoid oriin (ORI) is the basic structure for its anticancer activity, and esterification of the 14 hydroxyl group in the D-ring enhances its anticancer activity. Esterification of the 14 hydroxyl group in the D-ring enhances its anticancer activity [9]. Structural modification and optimization can not only alter the anticancer activity of a drug, but also reduce its side effects. 4-HPR, a vitamin A derivative, is susceptible to side effects such as skin dryness and dark adaptation disorder, although its combination with RA induces an increase in the differentiation of cancer cells. Studies have shown that these side effects can be significantly reduced by modifying the structure of 4-HPR, preserving key components and optimizing others. For example, methylaminophenol (p-MAP) retains its potency and has fewer side effects, while dodecylaminophenol (p-DDAP) not only reduces the side effects, but also exhibits stronger anticancer activity [10]. Low bioavailability and poor water solubility can also be improved by structural modifications. For example, glycosylation modification of ORIs can significantly improve their water solubility and bioavailability [11]. Since cancer cells have a high demand for sugar intake, glycosylated drugs are more easily absorbed by cancer cells, thus improving targeting [12]. In addition to glycosylation, modifications such as polyethylene glycolization and esterification can be used to further improve water solubility and increase bioavailability.

4.2. Application of nanotechnology

Nanotechnology plays an important role in improving the bioavailability and targeting of terpenoids. Nanodelivery systems not only improve the water solubility of terpenoids, but also provide protection against rapid degradation in the body. In addition, nanotechnology can control the release of terpenoids by designing pH-sensitive, temperature-sensitive, or enzyme-sensitive carriers, thereby improving the persistence and targeting of efficacy. Zhu et al prepared Rg3-PTX-Lps by preparing ginsenoside Rg3 as a liposomal carrier and piggybacking it with paclitaxel (PTX) [13].The study showed that Rg3-PTX-Lps exhibited good targeting in xenotumor grafting models and was able to inhibit tumors and regulate the tumor microenvironment effectively. Natural products of plant origin usually have low bioavailability and are difficult to accumulate in cells, but the nanoparticle delivery system can help to improve the concentration and stability of drugs in cells by controlling the release rate. Nanoparticles can passively accumulate in tumor or inflammatory tissues through the Enhanced Permeation and Retention Effect (EPR effect), thus improving drug targeting. In addition, nanoparticles can be actively modified with specific ligands such as antibodies, peptides, or small molecules that bind specifically to receptors on the surface of target cells, enabling active targeting. For example, Zhou et al. significantly improved drug targeting by constructing nanoparticles camouflaged by lung cancer cell membranes [14].Zhu et al. further developed chimeric antigen receptor T (CAR-T) cell-derived exosomes and fused them with lung-targeted liposomes to design hybrid nanovesicles named Lip-CExo@PTX for lung cancer immunotherapy, which successfully improved drug specificity and efficacy [15]. Nanocarriers can also be designed to respond to specific conditions in the tumor microenvironment (e.g., pH, enzymes, temperature, or redox state), ensuring that terpenoids are released only under specific conditions, thus further improving drug targeting and therapeutic efficacy.

DOI: 10.54254/2753-8818/75/2024.LA19342

5. Challenges and future perspectives of terpenoids in the clinic

5.1. Key issues in clinical application

Although terpenoids possess powerful anticancer effects and a wide range of targets of action, their performance in clinical applications has been less than satisfactory. Although these compounds generally have low toxicity, their toxic effects on normal cells become significant at higher concentrations. In addition, terpenoids are poorly targeted, and some sesquiterpenoids have particularly severe off-target effects, which may cause unwanted damage to normal tissues and cells, thus limiting their use in clinical applications [16]. Poor drug stability is also one of the major challenges for terpenoids. Many terpenoids are not stable enough in vivo and are susceptible to degradation by metabolic enzymes, which rapidly transforms them into inactive metabolites, leading to their low bioavailability. This metabolic instability makes it difficult to maintain the effective concentration of the drug in the body, reducing its therapeutic effect. In addition, the metabolic pathways of terpenoids may differ significantly between individuals, resulting in individual differences in patient response to the drugs, making clinical application more challenging. Therefore, in order to fully utilize the anticancer potential of terpenoids, there is a need to develop more precise and stable drug delivery systems, as well as to improve their targeting to ensure that the drugs are able to effectively act on cancer cells without damaging normal tissues. These improvements are essential to realize the clinical translation of terpenoids.

5.2. Future Research Directions

Terpenoids greatly limit their use in clinical applications due to low bioavailability and poor targeting. Therefore, future research should focus on solving these key difficulties. First, new drug delivery systems can be developed to reduce toxic side effects, improve targeting and achieve controlled release. In addition, by modifying the structure of terpenoids, their water solubility and bioavailability can be improved, thus enhancing the efficacy of the drugs. In addition to structural modifications, novel terpenoids with higher anticancer activity and lower side effects can be designed. Meanwhile, the discovery of terpenoids with new targets and new anticancer mechanisms is also an important direction for future research, which will help to expand the application scope of terpenoids and improve therapeutic effects. The potential anticancer effects of terpenoids that have already been used in clinical applications can also be further explored. Terpenoids should also be combined with other therapies to enhance their anti-cancer effects. For example, certain terpenoids can increase the sensitivity of tumor cells to immunotherapy, and combining them with immunotherapy can yield better results. In addition, terpenoids such as curcumin and piperine, when used in combination with radiotherapy, not only enhance the sensitivity of cancer cells to radiation, but also protect normal cells from radiation damage. In the future, it is necessary to further optimize the drug delivery system, study its multi-pathway anti-cancer mechanism, optimize the dosage, and evaluate the toxicity and safety. Meanwhile, finding suitable models to evaluate the efficacy of drugs is also an important step to ensure successful translation.

6. Conclusion

Each figure should have a brief caption describing it and, if necessary, a key to interpret the various lines and symbols on the terpenoids are compounds derived from natural products that demonstrate great potential in cancer therapy due to their wide range of biological activities and multi-targeted anti-cancer mechanisms. Not only do terpenoids fight cancer by conventional methods such as inducing apoptosis, inhibiting proliferation, and reversing drug resistance in cancer cells, but some of these compounds also increase the immunosensitivity of tumor cells or induce tumor cell differentiation to resist cancer, and terpenoids have demonstrated significant therapeutic efficacy in a variety of cancer models. However, despite positive results in laboratory studies, clinical translation of terpenoids continues to face many challenges, with the structure of many terpenoids in clinical trials differing dramatically from pre-tests, and suitable clinical models are often unavailable. The complex structure of terpenoids limits their synthesis to large-scale synthesis and the complex structure of terpenoids often makes it difficult to

DOI: 10.54254/2753-8818/75/2024.LA19342

study the relationship between drug activity and structure. The poor targeting of terpenoids leads to the killing of normal cells at high concentrations, and the poor efficacy caused by low bioavailability are the key problems limiting their application in the clinic.

Future research should focus on how to optimize the structure of terpenoids through chemical modifications to improve their water solubility, bioavailability and targeting. Alternatively, the structure of terpenoids can be studied to design derivatives with higher drug activity and fewer side effects. Meanwhile, the development of nanotechnology provides an effective and reliable way to improve drug delivery efficiency, combining liposomes, nanoparticles, and other delivery systems to encapsulate the drug to prevent degradation by various metabolic enzymes, which significantly improves the stability and efficacy of terpenoids in the body. In addition, advances in biotechnology, such as high-throughput screening and 3D cell culture technologies, have provided new tools for studying the specific targets of terpenoids, which are expected to accelerate their preclinical testing and translation into applications. Overall, terpenoids have great anticancer potential, but their clinical applications require further research and development. Optimizing their drug properties through the combination of nanotechnology and biotechnology will help to overcome the current limitations and bring more choices and possibilities for future cancer treatment.

References

[1] Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249

[2] Kamran S, Sinniah A, Abdulghani MAM, Alshawsh MA. Therapeutic Potential of Certain Terpenoids as Anticancer Agents: A Scoping Review. Cancers. 2022; 14(5):1100.

[3] Deb, D.D.; Parimala, G.; Devi, S.S.; Chakraborty, T. Effect of thymol on peripheral blood mononuclear cell PBMC and acute promyelotic cancer cell line HL-60. Chem. Biol. Interact. 2011, 193, 97–106.

[4] Rivera, E., & Gomez, H. (2010). Chemotherapy resistance in metastatic breast cancer: the evolving role of ixabepilone. Breast Cancer Research, 12(Suppl 2), S2.

[5] Tu Y, Zhang W, Fan G, et al. Paclitaxel-loaded ROS-responsive nanoparticles for head and neck cancer therapy. Drug Deliv. 2023;30(1):2189106. doi:10.1080/10717544.2023.2189106

[6] Xu, H., Van der Jeught, K., Zhou, Z., Zhang, L., Yu, T., Sun, Y., Li, Y., Wan, C., So, K. M., Liu, D., Frieden, M., Fang, Y., Mosley, A. L., He, X., Zhang, X., Sandusky, G. E., Liu, Y., Meroueh, S. O., Zhang, C., Wijeratne, A. B., … Lu, X. (2021). Atractylenolide I enhances responsiveness to immune checkpoint blockade therapy by activating tumor antigen presentation. The Journal of clinical investigation, 131(10), e146832.

[7] Wang Y, Zhang Z, Cheng Z, Xie W, Qin H, Sheng J. Astragaloside in cancer chemoprevention and therapy. Chin Med J (Engl). 2023;136(10):1144-1154.

[8] Noriko Takahashi, Daisuke Saito, Shinya Hasegawa, Masahiro Yamasaki, Masahiko, Imai, Vitamin A in health care: Suppression of growth and induction of differentiation in cancer cells by vitamin A and its derivatives and their mechanisms of action, Pharmacology & Therapeutics, Volume 230, 2022, 107942, ISSN 0163-7258

[9] Varoni, E. M., Lo Faro, A. F., Sharifi-Rad, J., & Iriti, M. (2016). Anticancer molecular mechanisms of resveratrol. Frontiers in Nutrition,

[10] Tong, Yangliu et al. “Insight on structural modification, biological activity, structure-activity relationship of PPD-type ginsenoside derivatives.” Fitoterapia (2022): 105135 .

[11] Zhang Y, Wang S, Dai M, Nai J, Zhu L, Sheng H. Solubility and Bioavailability Enhancement of Oridonin: A Review. Molecules. 2020; 25(2):332.

[12] Noriko Takahashi, Daisuke Saito, Shinya Hasegawa, Masahiro Yamasaki, Masahiko Imai, Vitamin A in health care: Suppression of growth and induction of differentiation in cancer cells by vitamin A and its derivatives and their mechanisms of action, Pharmacology & Therapeutics, Volume230, 2022, 107942, ISSN0163-7258.

DOI: 10.54254/2753-8818/75/2024.LA19342

[13] Dalziel, M.; Crispin, M.; Scanlan, C.N.; Zitzmann, N.; Dwek, R.A. Emerging principles for the therapeutic exploitation of glycosylation. Science 2014, 343, 37–45

[14] Szablewski, L. Expression of glucose transporters in cancers. Biochim. Biophys. Acta. 2013, 1835, 164–169.

[15] Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells, Journal of Advanced Research, Volume 49, 2023, Pages 159-173, ISSN 2090-1232

[16] Jiahan Zhou, Shengli Wan, Yuesong Wu, Haiyang Hu, Yang Liu, Zuyue Liao, Mengyao Xu, Jianming Wu, Qingze Fan, Cancer cell membrane-camouflaged paclitaxel/PLGA nanoparticles for targeted therapy against lung cancer, Biomedicine & Pharmacotherapy, Volume 177, 2024, 117102, ISSN 0753-3322