Application of Polyphenols in Cancer Therapy

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The characteristics of polyphenols in modulating redox homeostasis have been widely applied in cancer prevention and treatment, which lays the basis for the discovery and development of natural anticancer drugs. Indeed, many polyphenols have been explored in preclinical or clinical trials, but the drawbacks of polyphenols generally disturb their versatile properties in clinical settings

polyphenol oxidative stress ROS cancer therapy redox

1. Introduction

Specific structures, such as phenolic hydroxyl groups and the catechol ring of polyphenols, make them easy to oxidize [1], which greatly deteriorates their stability and increases the probability of degradation [2]. In addition, their poor water solubility, their inadequate bioavailability, and more importantly, the nonspecific selectivity of polyphenols limit their pharmacological applications [3][4]. Moreover, the single use of polyphenols always compromises their limited cytocidal effect [5]. Robust strategies have been developed to surmount these limitations to accelerate the efficient implementation of CHM-derived polyphenols for cancer treatment (**Figure 1**).

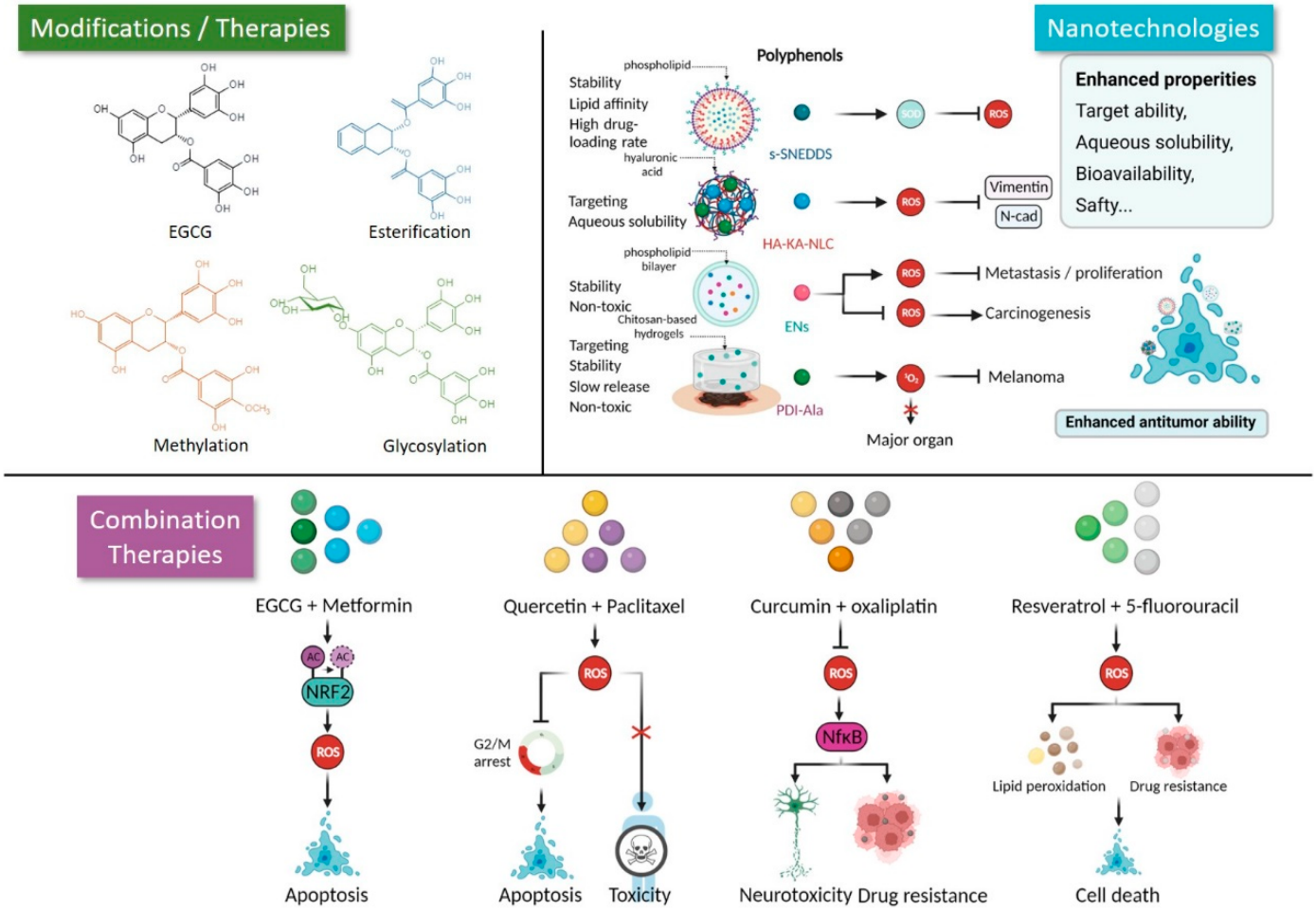

Figure 1. Novel strategies promote the application of polyphenols in cancer therapy. Structural modifications, such as esterification, methylation, and glycosylation, protect polyphenols from rapid degradation and promote their bioactivities. Nanotechnologies can make up the inherent limitations of polyphenols and support targeting delivery of them to specific tumor lesions with minor side effects. Combination therapies achieve efficient tumor eliminate via enhanced ROS-mediated mechanisms.

2. Modification

Structural modifications, such as esterification, methylation, and glycosylation, can avoid degradation and enhance the bioactivities of polyphenols. For example, the esterification of EGCG through the substitution of hydroxyl groups with the chain of fatty acids not only increased lipophilicity, but also promoted its antioxidant capacity via enhanced hydrogen atom donation [6]. Similarly, a lipophilized EGCG derivative (LEGCG) synthesized by a partial esterification reaction (an enzymatic esterification model) of EGCG with lauric acid improved its bioactivity, including anti-proliferation and pro-apoptosis effects [7]. In addition, the methylation of EGCG, which alters the phenolic hydroxyl groups of the EGCG benzene ring into methyl ether, could amend its oral absorption rate and blood stability. For instance, the in vivo bioavailability and stability of EGCG was greatly enhanced when the hydroxyl groups were replaced by more stable methoxy groups [8]. Similarly, the bioavailability of methylated EGCG was higher than that of free or unmethylated EGCG [9]. The glycosylation of polyphenols can improve their

solubility and stability and protect these compounds from oxidants, light degradation, and hostile gastrointestinal conditions [10][11]. Intriguingly, the glycosylated EGCG could act as a prodrug and first be deglycosylated at the intestinal surface before diffusing into enterocytes, thereby increasing the stability of EGCG during processing, storage, and gut transit after ingestion [12]. Moreover, the modifications for polyphenols could enhance the purification efficiency, prolong the preservation time, and avoid degradation in elevated large-scale production and commercialization [13][14][15]. Taken together, the modification of polyphenols evades rapid degradation and enhances their accessibility, thus providing rational strategies to accelerate the application of polyphenols in cancer treatment.

3. Nano Strategies

Recent evidence has shown that nano strategies can aid in overcoming polyphenols' inherent drawbacks, including their low water solubility, poor stability, and nontargeting ability [16][17]. A myriad of nano strategies has been well established for improving pharmacokinetic properties under polyphenol administration [18][19]. Some nanocarriers, such as nanoparticles, liposomes, hydrogels, and extracellular vehicles, are widely applied to deliver polyphenols for cancer treatment [20][21][22]. The nanostructured lipid carrier can encapsulate kaempferol to optimize its low aqueous solubility and poor bioavailability [23]. After being modified with hyaluronic acid (HA), the HA-KA-NLC nanoplatform could target NSCLC cells by recognizing highly expressed CD44, thus exhibiting more efficient inhibition of their proliferation and EMT than free kaempferol administration. Indeed, these nano strategies strengthened redox regulation, which synergizes with the enhanced bioavailability to greatly improve therapeutic efficiency. One recent study reported a solid self-nanoemulsifying drug delivery system (s-SNEDDS) loaded with resveratrol and tamoxifen to treat breast cancer [24]. The s-SNEDDS team not only improved the bioavailability of resveratrol, but also sensitized tamoxifen-mediated chemotherapy and exhibited satisfactory suppression of MCF-7 breast cancer cells by triggering resveratrol-induced ROS elimination and SOD activation. In addition, a tannic acid-loaded dual antioxidant-photosensitizing hydrogel system was established to protect against human melanoma. In this nanosystem, chitosan-based hydrogels were designed using tannic acid as an antioxidant cross-linker and loaded with photosensitizer PDI-Ala, in which the tannic acid controlled the ROS generation and minimized the side effects of singlet oxygen synergistically with PDI-Ala boosted photodynamic therapy [25]. Recently, natural exosome-like nanovesicles (ENs) have endured much investigation as novel carriers and therapeutic agents. In Zu's study, ENs extracted from green tea leaves were rich in polyphenols such as EGCG, quercetin, and myricetin and exhibited distinct efficiency in preventing AOM- and DSS-induced colorectal carcinogenesis in a mouse model by maintaining intracellular redox homeostasis [26]. Similarly, tea flower-derived ENs could inhibit breast cancer metastasis by stimulating ROS amplification [27]. Taken together, nano strategies ideally tackle the limitations of polyphenols, making them promising agents for cancer treatment.

4. Combination with Other Agents

Strategies to combine polyphenols with other agents play important roles in preclinical evaluation and clinical implementation, including amplifying ROS-mediated therapeutic efficiency and avoiding chemotherapy-induced

side effects [28]. The combinational use of EGCG with metformin, a classical antidiabetic drug, stimulated intracellular ROS accumulation induced by EGCG (100 μM) through the modulation of Sirtuin 1-dependent deacetylation on NRF2, thus augmenting the anticancer effect of EGCG in NSCLC treatment [29]. Indeed, the combination of polyphenols with first-line chemotherapies such as paclitaxel, 5-fluorouracil, and oxaliplatin could not only augment the cytocidal function but also reduce the side effects of these chemotherapies [30][31]. In addition, combined treatment with quercetin and paclitaxel could significantly inhibit proliferation and migration and evoke apoptosis via increased ROS generation, as well as attenuate the side effects of paclitaxel in PC-3 prostate cancer cells [32]. Similarly, the combination of curcumin also sensitizes cancer cells to oxaliplatin and alleviates oxaliplatin-induced peripheral neuropathic pain by inhibiting the oxidative stress-mediated activation of NF-κB [33][34][35]. Interestingly, a recent phase I trial showed the safety, tolerability, and feasibility of administering curcumin as an adjunct to FOLFOX (5-fluorouracil, folinic acid, and oxaliplatin) chemotherapy in patient-derived colorectal or liver metastases cancer [NCT01490996]. Alternatively, resveratrol exhibited a synergetic effect with 5-fluorouracil to induce an imbalance in cellular antioxidant activities and subsequent intracellular ROS accumulation and lipid peroxides, thus leading to a significant decrease in long-term colon cell survival [36]. In summary, these novel strategies ingeniously alleviate the predicament of polyphenols and enhance the feasibility of developing new agents with redox regulation's ability to overcome cancer progression.

References

1. Pietta, P.G. Flavonoids as antioxidants. J. Nat. Prod. 2000, 63, 1035–1042.
2. Ouyang, J.; Zhu, K.; Liu, Z.; Huang, J. Prooxidant Effects of Epigallocatechin-3-Gallate in Health Benefits and Potential Adverse Effect. Oxidative Med. Cell. Longev. 2020, 2020, 9723686.
3. Costa, C.; Tsatsakis, A.; Mamoulakis, C.; Teodoro, M.; Briguglio, G.; Caruso, E.; Tsoukalas, D.; Margina, D.; Dardiotis, E.; Kouretas, D.; et al. Current evidence on the effect of dietary polyphenols intake on chronic diseases. Food Chem. Toxicol. 2017, 110, 286–299.
4. Fraga, C.G.; Galleano, M.; Verstraeten, S.V.; Oteiza, P.I. Basic biochemical mechanisms behind the health benefits of poly-phenols. Mol. Asp. Med. 2010, 31, 435–445.
5. Saunders, N.A.; Simpson, F.; Thompson, E.W.; Hill, M.M.; Endo-Munoz, L.; Leggatt, G.; Minchin, R.; Guminski, A. Role of intratumoural heterogeneity in cancer drug resistance: Molecular and clinical perspectives. EMBO Mol. Med. 2012, 4, 675–684.
6. Zhong, Y.; Shahidi, F. Lipophilized Epigallocatechin Gallate (EGCG) Derivatives as Novel Antioxidants. J. Agric. Food Chem. 2011, 59, 6526–6533.
7. Chen, J.; Zhang, L.; Li, C.; Chen, R.; Liu, C.; Chen, M. Lipophilized Epigallocatechin Gallate Derivative Exerts Anti-Proliferation Efficacy through Induction of Cell Cycle Arrest and Apoptosis on DU145 Human Prostate Cancer Cells. Nutrients 2019, 12, 92.

8. Forester, S.C.; Lambert, J.D. The catechol-O-methyltransferase inhibitor, tolcapone, increases the bioavailability of un-methylated (−)-epigallocatechin-3-gallate in mice. J. Funct Foods 2015, 17, 183–188.
9. Zhang, M.; Zhang, X.; Ho, C.T.; Huang, Q. Chemistry and Health Effect of Tea Polyphenol (-)-Epigallocatechin 3- O-(3- O-Methyl)gallate. J. Agric. Food Chem. 2019, 67, 5374–5378.
10. Kim, J.; Nguyen, T.T.H.; Kim, N.M.; Moon, Y.-H.; Ha, J.-M.; Park, N.; Lee, D.-G.; Hwang, K.-H.; Park, J.-S.; Kim, D. Functional Properties of Novel Epigallocatechin Gallate Glucosides Synthesized by Using Dextransucrase from Leuconostoc mesenteroides B-1299CB4. J. Agric. Food Chem. 2016, 64, 9203–9213.
11. Méndez-Líter, J.A.; Pozo-Rodríguez, A.; Madruga, E.; Rubert, M.; Santana, A.G.; de Eugenio, L.I.; Sánchez, C.; Martínez, A.; Prieto, A.; Martínez, M.J. Glycosylation of Epigallocatechin Gallate by Engineered Glyco-side Hydrolases from Talaromyces amestolkiae: Potential Antiproliferative and Neuroprotective Effect of These Molecules. Antioxidants 2022, 11, 1325.
12. Gonzalez-Alfonso, J.L.; Leemans, L.; Poveda, A.; Jimenez-Barbero, J.; Ballesteros, A.O.; Plou, F.J. Efficient α-Glucosylation of Epigallocatechin Gallate Catalyzed by Cyclodextrin Glucanotransferase from Thermoanaerobacter Species. J. Agric. Food Chem. 2018, 66, 7402–7408.
13. Boateng, I.D. Recent processing of fruits and vegetables using emerging thermal and non-thermal technologies. A critical review of their potentialities and limitations on bioactives, structure, and drying performance. Crit. Rev. 2022, 1–35.
14. Rambaran, T.F. A patent review of polyphenol nano-formulations and their commercialization. Trends Food Sci Tech. 2022, 120, 111–122.
15. Cao, H.; Saroglu, O.; Karadag, A.; Diaconeasa, Z.; Zoccatelli, G.; Conte-Junior, C.A.; Gonzalez-Aguilar, G.A.; Ou, J.; Bai, W.; Zamarioli, C.M.; et al. Available technologies on improving the stability of polyphenols in food processing. Food Front. 2021, 2, 109–139.
16. De Oliveira, T.V.; Stein, R.; de Andrade, D.F.; Beck, R.C.R. Preclinical studies of the antitumor effect of curcumin-loaded polymeric nanocapsules: A systematic review and meta-analysis. Phytother. Res. 2022, 36, 3202–3214.
17. Gugleva, V.; Ivanova, N.; Sotirova, Y.; Andonova, V. Dermal Drug Delivery of Phytochemicals with Phenolic Structure via Lipid-Based Nanotechnologies. Pharmaceuticals 2021, 14, 837.
18. Bohara, R.A.; Tabassum, N.; Singh, M.P.; Gigli, G.; Ragusa, A.; Leporatti, S. Recent Overview of Resveratrol’s Beneficial Effects and Its Nano-Delivery Systems. Molecules 2022, 27, 5154.
19. Lu, S.; Tian, H.; Li, L.; Li, B.; Yang, M.; Zhou, L.; Jiang, H.; Li, Q.; Wang, W.; Nice, E.C.; et al. Nanoengineering a Zeolitic Imidazolate Framework-8 Capable of Manipulating Energy Metabolism against Cancer Chemo-Phototherapy Resistance. Small 2022, 18, e2204926.

20. Yu, H.; Palazzolo, J.S.; Ju, Y.; Niego, B.; Pan, S.; Hagemeyer, C.E.; Caruso, F. Polyphenol-Functionalized Cubosomes as Thrombolytic Drug Carriers. Adv. Health Mater. 2022, 11, e2201151.
21. Hafez Ghoran, S.; Calcaterra, A.; Abbasi, M.; Taktaz, F.; Nieselt, K.; Babaei, E. Curcumin-Based Nanoformulations: A Promising Adjuvant towards Cancer Treatment. Molecules 2022, 27, 5236.
22. Soleti, R.; Andriantsitohaina, R.; Martinez, M.C. Impact of polyphenols on extracellular vesicle levels and effects and their properties as tools for drug delivery for nutrition and health. Arch. Biochem. Biophys. 2018, 644, 57–63.
23. Ma, Y.; Liu, J.; Cui, X.; Hou, J.; Yu, F.; Wang, J.; Wang, X.; Chen, C.; Tong, L. Hyaluronic Acid Modified Nanostructured Lipid Carrier for Targeting Delivery of Kaempferol to NSCLC: Preparation, Optimization, Characterization, and Performance Evaluation In Vitro. Molecules 2022, 27, 4553.
24. Shrivastava, N.; Parikh, A.; Dewangan, R.P.; Biswas, L.; Verma, A.K.; Mittal, S.; Ali, J.; Garg, S.; Baboota, S. Solid Self-Nano Emulsifying Nanoplatform Loaded with Tamoxifen and Resveratrol for Treatment of Breast Cancer. Pharmaceutics 2022, 14, 1486.
25. Azadikhah, F.; Karimi, A.R.; Yousefi, G.H.; Hadizadeh, M. Dual antioxidant-photosensitizing hydrogel system: Cross-linking of chitosan with tannic acid for enhanced photodynamic efficacy. Int. J. Biol. Macromol. 2021, 188, 114–125.
26. Zu, M.; Xie, D.; Canup, B.S.; Chen, N.; Wang, Y.; Sun, R.; Zhang, Z.; Fu, Y.; Dai, F.; Xiao, B. ‘Green’ nanotherapeutics from tea leaves for orally targeted prevention and alleviation of colon diseases. Biomaterials 2021, 279, 121178.
27. Chen, Q.; Li, Q.; Liang, Y.; Zu, M.; Chen, N.; Canup, B.S.; Luo, L.; Wang, C.; Zeng, L.; Xiao, B. Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer via ROS generation and microbiota modulation. Acta Pharm. Sin. B 2022, 12, 907–923.
28. Mereles, D.; Hunstein, W. Epigallocatechin-3-gallate (EGCG) for clinical trials: More pitfalls than promises? Int. J. Mol. Sci. 2011, 12, 5592–5603.
29. Yu, C.; Jiao, Y.; Xue, J.; Zhang, Q.; Yang, H.; Xing, L.; Chen, G.; Wu, J.; Zhang, S.; Zhu, W.; et al. Metformin Sensitizes Non-small Cell Lung Cancer Cells to an Epigallocatechin-3-Gallate (EGCG) Treatment by Suppressing the Nrf2/HO-1 Signaling Pathway. Int. J. Biol. Sci. 2017, 13, 1560–1569.
30. Du, D.; Tang, X.; Li, Y.; Gao, Y.; Chen, R.; Chen, Q.; Wen, J.; Wu, T.; Zhang, Y.; Lu, H.; et al. Senotherapy Protects against Cisplatin-Induced Ovarian Injury by Removing Senescent Cells and Alleviating DNA Damage. Oxidative Med. Cell. Longev. 2022, 2022, 9144644.
31. Schwingel, T.E.; Klein, C.P.; Nicoletti, N.F.; Dora, C.L.; Hädrich, G.; Bica, C.G.; Lopes, T.G.; Da Silva, V.D.; Morrone, F.B. Effects of the compounds resveratrol, rutin, quercetin, and quercetin

nanoemulsion on oxaliplatin-induced hepatotoxicity and neurotoxicity in mice. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 2014, 387, 837–848.

32. Zhang, X.; Huang, J.; Yu, C.; Xiang, L.; Li, L.; Shi, D.; Lin, F. Quercetin Enhanced Paclitaxel Therapeutic Effects Towards PC-3 Prostate Cancer Through ER Stress Induction and ROS Production. OncoTargets Ther. 2020, 13, 513–523.
33. Jalili-Nik, M.; Soltani, A.; Moussavi, S.; Ghayour-Mobarhan, M.; Ferns, G.A.; Hassanian, S.M.; Avan, A. Current status and future prospective of Curcumin as a potential therapeutic agent in the treatment of colorectal cancer. J. Cell. Physiol. 2017, 233, 6337–6345.
34. Zangui, M.; Atkin, S.L.; Majeed, M.; Sahebkar, A. Current evidence and future perspectives for curcumin and its analogues as promising adjuncts to oxaliplatin: State-of-the-art. Pharmacol. Res. 2019, 141, 343–356.
35. Zhang, X.; Guan, Z.; Wang, X.; Sun, D.; Wang, D.; Li, Y.; Pei, B.; Ye, M.; Xu, J.; Yue, X. Curcumin Alleviates Oxaliplatin-Induced Peripheral Neuropathic Pain through In-hibiting Oxidative Stress-Mediated Activation of NF-κB and Mitigating Inflammation. Biol. Pharm. Bull. 2020, 43, 348–355.
36. Santandreu, F.M.; Valle, A.; Oliver, J.; Roca, P. Resveratrol potentiates the cytotoxic oxidative stress induced by chemo-therapy in human colon cancer cells. Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol. 2011, 28, 219–228.