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Review Articles

Harnessing the capacity of phytochemicals to enhance immune checkpoint inhibitor therapy of cancers: A focus on brain malignancies

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Highlights

- Brain cancers, particularly glioblastoma multiforme (GBM) are challenging health issues.
- Immunotherapy is an emerging area of investigation in cancer treatment.
- Phytochemicals show good effectiveness and making them suitable to develop immune checkpoint inhibitors (ICIs).
- We discussed the involvement of immune checkpoints in cancer pathology.
- We also summarized the application of phytochemicals in modulating immune checkpoints in brain tumors.

Abstract

Brain cancers, particularly glioblastoma multiforme (GBM), are challenging health issues with frequent unmet aspects. Today, discovering safe and effective therapeutic modalities for brain tumors is among the top research interests. Immunotherapy is an emerging area of investigation in cancer treatment. Since immune checkpoints play fundamental roles in repressing anti-cancer immunity, diverse immune checkpoint inhibitors (ICIs) have been developed, and some monoclonal antibodies have been approved clinically for particular cancers; nevertheless, there are significant concerns regarding their efficacy and safety in brain tumors. Among the various tools to modify the immune checkpoints, phytochemicals show good effectiveness and excellent safety, making them suitable candidates for developing better ICIs. Phytochemicals regulate multiple immunological checkpoint-related signaling pathways in cancer biology; however, their efficacy for clinical cancer immunotherapy remains to be established. Here, we discussed the involvement of immune checkpoints in cancer pathology and summarized recent advancements in applying phytochemicals in modulating immune checkpoints in brain tumors to highlight the state-of-the-art and give constructive prospects for future research.

Introduction

Developing novel anti-cancer modalities is still challenging for scientists due to the complicated and multidimensional nature of neoplasms [1]. This challenge is even more severe in the case of brain tumors, particularly glioblastoma multiforme (GBM), due to their highly malignant character and difficult targeted drug delivery [2,3]. Despite the introduction of multiple authorized therapies in the clinic, the prognosis of brain tumors is unfavorable, and patients often experience a short survival period along with a dismal quality of life [[4], [5], [6]]. Therefore, significant efforts are conducting to address the need for urgent development of proficient treatment approaches [[7], [8], [9]]. To that end, immunotherapy combined with improved drug delivery methods opens up a new avenue for developing effective tumor-fighting medicines harnessing the immune system [10].

Natural immune system failure in cancer therapy is related to immune checkpoint-mediated tolerance, in which immune activity is negatively regulated and cytotoxic T-cell defense is weakened [11]. Several immune checkpoints have been recognized, but cytotoxic T lymphocyte-associated protein-4 (CTLA-4) and programmed death-1 (PD-1) are more critical in terms of immune suppression [12]. Intriguingly, targeting immune checkpoints has changed cancer immunotherapy with encouraging results [13,14]. Suppression of PD-1 and/or CTLA-4, for instance, exhibited a remarkable promotion in progression-free survival (PFS) and overall survival (OS) rather than conventional chemotherapeutics in metastatic non-small-cell lung carcinoma

(NSCLC) [15]. Findings of a recent meta-analysis also confirmed the superior anti-cancer impacts of immune checkpoint inhibitor (ICI) therapy compared to non-ICI treatments [16]. It is even getting more interesting when the soluble CTLA-4 is introduced as a foretelling factor for hepatocellular tumor recurrence, making early-stage treatment possible [17]. To date, the FDA has approved some monoclonal antibodies (mAbs) inhibiting the immune checkpoints in certain malignancies; however, their efficacy and safety in treating brain tumors are still under question, and there is no clear answer for the mentioned problem since we are still standing in the middle of it and systematic research and clinical assessments are needed to develop unique strategies based on immune checkpoints modulation [[18], [19], [20]]. Indeed, the application of ICIs in treating brain malignancies like GBM is theoretically possible, but no medication has yet received complete approval [14,21]. Recruiting immunomodulatory phytochemicals is among the potential solutions to improve current immunotherapy approaches [22,23]. It has been demonstrated that various naturally bioactive substances extracted from medicinal herbals can affect tumor immune checkpoints, promoting anti-cancer immunity while possessing lower toxicity than mAbs [24]. These natural substances could be the origin of functional ingredients for developing safe and efficacious checkpoint inhibitors. The present paper conferred an updated overview of immune checkpoint modulation in cancer biology and focused on the recent advancements in the application of phytochemicals in improving the immune checkpoint therapy of brain cancers. We first highlighted the involvement of immune checkpoints in cancer biology and the advantages/drawbacks of immune checkpoint inhibition by considering currently approved drugs. Then, we discussed the potential of phytochemicals, e.g., apigenin, curcumin, and triptolide, in the development of ICIs with good efficacy and better safety in cancer immunotherapy.

Section snippets

Immune checkpoints in cancer biology

The immune system has a fundamental function in recognizing and eliminating precancerous and cancerous cells, called “immune surveillance,” relying mainly on the adaptive immunity powered by cellular and humoral elements activating cytotoxic $CD4^+$ and $CD8^+$ T lymphocytes. Innate immunity, done by natural killer (NK) cells, also participates in this process [25,26]. However, due to the distinctive and generally extensive mutational nature of malignancies, the balance between cancerous cells and…

Anti-cancer mechanisms of ICIs

The emergence of ICIs has metamorphosed the effectiveness of cancer immunotherapy and showed satisfactory impacts in cancer patients by suppressing CTLA-4 and PD-1 immune checkpoints. Due to the positive outcomes, several ICIs were authorized by the FDA for application in various malignancies, including breast, lung, and urothelial cancers, as well as melanoma and HCC [79]. In this section, we discussed the molecular mechanism behind the inhibition of each immune checkpoint in the context of…

Drawbacks of cancer ICI therapy

Since 2011, the FDA has approved several mAbs for repressing CTLA-4 (e.g., ipilimumab) and/or PD-1 (e.g., cemiplimab and dostarlimab) for cancer immunotherapy that is commonly used in cancer patients with dismal prognosis when choice treatments fail [79]. Furthermore, many patients receiving mAb ICIs are categorized as non-responders or progress following primary response due to ambiguous resistance mechanisms. Several factors like TME properties, the existence of TILs and tumor-associated…

Phytochemicals as promising immune checkpoint inhibitors

Phytochemicals are the foundation of many anti-cancer medications that are now being tested in clinical settings [131,132]. They also represent a promising origin for developing novel cancer therapies in the future. Extracts from plants include natural compounds with a broad range of biological functions in the human body. The anti-cancer impacts of phytochemicals have been substantiated by numerous research in the areas of clinical pharmacology, molecular sciences, clinical biochemistry, and…

Concluding remarks and future perspectives

The identification of tumor cells by T cells may be inhibited when immune checkpoint molecules interact with one another in the TME. This results in a diminished anti-tumor immune response. Accordingly, the use of ICIs as potential cancer treatments is gaining traction as exciting new therapeutic alternatives. Nevertheless, regulating the immune system with currently available ICIs still confronts challenges, including significant immunogenic negative effects as well as a failure to respond…

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Declaration of competing interest

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

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