The Use of Phytochemicals to Improve the Efficacy of Immune Checkpoint Inhibitors: Opportunities and Challenges

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Abstract: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and reshaped medical oncology practice over the past decade. However, despite unprecedented and durable clinical responses, most patients eventually fail to respond to ICI therapy due to primary or acquired resistance. There is a great need for complementary alternative medicine, such as botanicals and nutritional supplements, because of their capability to modulate a myriad of molecular mechanisms to prevent immunotherapy resistance and reduce its adverse effects. Mounting evidence suggests that phytochemicals, biologically active compounds derived from plants, can favorably regulate key signaling pathways involved in tumor development and progression. In addition, phytochemicals have been found to exert antitumor effects by altering the expression of checkpoint inhibitors of the immune response. The immunomodulatory activity of phytochemicals in the tumor microenvironment has recently received immense interest. Based on these immunomodulatory activities, phytochemicals could be candidates for combination with ICIs in future clinical studies. The current review focuses on the available evidence for combining phytochemicals with a discussion on the promising opportunities to enhance the efficacy of immune checkpoint inhibitors and potential challenges resulting from these combinations.

Keywords: phytochemicals; immune checkpoint inhibitors; immunotherapy; PD-1; PD-L1; CTLA-4

1. Introduction

Immune checkpoint inhibitors (ICIs) have dramatically changed the oncology landscape and become a vital part of cancer care [1]. ICIs have demonstrated efficacy in several scenarios, such as monotherapy, combination with chemotherapy or targeted therapy, and first-line and subsequent treatment lines in almost all cancers [2–4]. The monoclonal antibodies against PD-1 and PD-L1 are the foundations of modern immunotherapy, and currently, eight anti-PD-1/PD-L1 agents are licensed in several different indications [5,6]. Still, many patients do not respond to ICIs, and resistance is inevitable in previously responding patients. Baseline and on-treatment immune dysregulation and immune exhaustion are the main proposed reasons for this treatment resistance [7]. There is an urgent need for novel approaches, such as combinations, to modify tumor microenvironments and mobilize the immune system to fight against tumors more effectively.

Phytochemicals are plant-based bioactive chemicals with diverse health-promoting effects, including cancer prevention. Removal of antioxidant stress, prevention of DNA
damage, and promotion of apoptosis after DNA damage with phytochemicals are hypothesized to be the main mechanisms of the anticancer effects of phytochemicals [8–10]. However, besides the antioxidant effects, the impacts of phytochemicals on the immune system could be instrumental for anticancer effects, and the immunomodulatory effects of phytochemicals in tumor microenvironments have recently received a lot of interest [11,12]. The preclinical evidence has demonstrated that plant-based polysaccharides, phenols, and silibinin could improve immunosuppression in the tumor microenvironments by inhibiting myeloid-derived suppressor cell accumulation and CD4-T lymphocyte expansion, as well as change the PD-L1 expression levels in tumor microenvironments [13]. Additionally, metabolomic studies have pointed out the possible role of phytochemicals as the mediators of the immune system and gut microbiome cross-talk, as evidenced by the increased response rates in ICI-treated melanoma patients with increased anacardic acid levels. Beneficial commensal bacteria such as *Faecalibacterium prausnitzii* and *Bacteroides thetaiotamicron* were also enriched in ICI responders, supporting an association between phytochemicals and a healthier gut microbiome and driving a better immune response [14].

Based on these immunomodulatory properties, phytochemicals could be candidates for combination therapies with anti-PD-1/anti-PD-L1 agents. Both preclinical data and data from metabolome and microbiome analyses have pointed out the role of phytochemicals in mediating immunotherapy efficacy. However, the evidence is limited, with conflicting results. Therefore, we aim to review the available evidence on the phytochemical and ICI combinations and to discuss the opportunities to improve ICI efficacy and possible challenges resulting from these combinations.

### 2. Literature Search and Review Structure

We conducted a literature review from the PubMed, Medline, and Embase databases to perform filtering of published studies. The MeSH search terms were “immunotherapy” OR “immune checkpoint” AND “PD-1” OR “PD-L1” OR “CTLA-4” OR “phytochemical” OR “phytonutrient” OR “microbiome”. Additionally, we conducted PubMed searches for the individual phytochemical names. We included original articles in the English language that evaluate the effects of phytochemicals on immune checkpoints, ICI and phytochemical combinations, and the association between the microbiome and ICI efficacy.

The review consisted of four sections. The first section was about “Preclinical Evidence Evaluating the Effects of Phytochemicals on Immune Checkpoints”, for which we reviewed the available evidence on the effects of phytochemicals on immune checkpoints in cell line and animal models. In the second section of the review, “The Preclinical Studies Evaluating the Efficacy of Phytochemical and Immune Checkpoint Inhibitor Combinations”, we reviewed the studies evaluating phytochemical and ICI combinations. Due to a lack of human data, we included preclinical studies only. In “The Clues from the Microbiome Studies on the Benefit of Phytochemicals in Immunotherapy Efficacy”, we reviewed the association between phytochemicals and the microbiome and the therapeutic opportunities that stemmed from phytochemicals’ effects on the microbiome. In the last part of the review, we discussed the further clinical perspectives and challenges related to phytochemical and ICI combinations in the clinic and areas needing improvement to develop effective combinations.

### 3. Preclinical Evidence Evaluating the Effects of Phytochemicals on Immune Checkpoints

Although the effects of phytochemicals on the immune system and tumor microenvironment have been extensively studied [12,15], the impact of phytochemicals on the immune checkpoints began receiving increased interest following ICIs’ entrance into clinical practice. Phytochemicals have been suggested to have the potential to modulate the therapeutic effects of immune checkpoint inhibitors through the regulation of several signaling pathways (Figure 1). Preclinical studies with variable phytochemicals were conducted on several tumor types, including NSCLC, breast cancer, colorectal cancer, hepatocellular cancer, melanoma, head and neck cancer, and glioblastoma (Table 1). While most studies...
have focused on phytochemicals’ effects on the PD-1 and PD-L1 pathways, one study reported the blockage of both PD-1/PD-L1 and the CTLA-4/CD80 interactions by the flavonoids eriodictyol, fisetin and quercetin liquiritigenin [16]. The phytochemicals mainly caused decreases in the tumor PD-L1 expression. In contrast, Z-guggulsterone, a phytosterol, increased PD-L1 mRNA expression and transcription in a dose-dependent manner via the activation of the AKT and ERK1/2 signaling pathways [17]. While the authors suggested that increased PD-L1 expression could be an opportunity to develop combinations with synergism, the increased PD-1 expression secondary to AKT and ERK1/2 activations could reduce ICI efficacy as a result of the pivotal roles of AKT and ERK1/2 activation in resistance to immunotherapy in clinical studies [18,19].

![Figure 1](image_url)  
**Figure 1.** Schematic figure representing some interactions between phytochemicals, T-cells, and cancer cells. Phytochemicals have been suggested to have the potential to modulate the therapeutic effects of immune checkpoint inhibitors and PD-L1 expression through the regulating of several signaling pathways, such as EGFR/Akt. Some phytochemicals can regulate PD-L1 expression, while others inhibit PD-L1 glycosylation or PD-L1/PD-1 binding, such as quercetin, saponins, and fisetin. Abbreviations: EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; MHC: major histocompatibility complex; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand 1 (PD-L1).

Interestingly, Phoenix dactylifera extract (including gallic acid, coffeic acid, and ellagic acid phytochemicals) increased cardiac and kidney PD-1 expressions in a mouse model exposed to Adriamycin [20]. The Phoenix dactylifera extract led to attenuated cardiotoxicity and nephrotoxicity secondary to decreased oxidative stress and apoptotic pressure. The authors suggested that increased PD-1 levels could protect from cardiotoxicity and nephrotoxicity via reduced oxidative stress and apoptotic pressure [20]. If their observations could be confirmed in clinical trials, the phytochemicals could be used for toxicity prevention in ICI-treated patients. Additionally, increased PD-1 expression and corresponding immuno-
suppression could be exercised as a strategy to prevent or mitigate immune-related adverse events by immunotherapy.

The STAT pathway was the other commonly affected pathway from phytochemicals, with five studies reporting STAT pathway aberrations in addition to changes in the PD-1/PD-L1 pathway [21–25]. While STAT1 and STAT2 involve the constitution of the anti-tumor response via cross-talks with IFN, STAT3 has pro-oncogenic and immunosuppressive properties [26]. Phytochemicals created a consistent inhibitory effect on the STAT3 pathway, and STAT3 down-regulation was among the drivers of PD-L1 suppression in several studies [22,25]. Contrary to the inhibition of immune-suppressive STAT3 by phytochemicals, Xu et al. demonstrated an inhibitory effect on STAT1 by apigenin, a flavonoid, and observed a greater decrease in PD-L1 by apigenin than curcumin secondary to more potent inhibition of STAT1 by apigenin [23]. These observations show that different phytochemicals could act differently on STAT proteins (immune-activating vs. immune-suppressive), and various classes of phytochemicals (i.e., flavonoid and non-flavonoid polyphenols) could have different potency on the tumor immune milieu (Figure 2). Further delineation of these interactions for individual phytochemicals is paramount to designing successful phytochemical and immunotherapy combinations.

**Figure 2.** Schematic figure reporting the main phytochemicals which have been tested as modulators of immune checkpoint inhibitors in cancer patients. The flavonoid polyphenols include, among others, icaritin, luteolin, bilberry anthocyanin, and melafolone. Non-flavonoid polyphenolic compounds include curcumin, gallic acid, gallotannin, and resveratrol, while terpenes include lycopene, diosgenin, and cryptotanshinone.
Table 1. The combined effect of dietary phytochemicals and immune checkpoint inhibitors on different types of cancer.

| Authors                  | Phytochemical Group     | Phytochemical Compound | Immune Checkpoint Inhibitor | Cancer Type          | Cancer Model                        | Mechanism of Effect                                                                                       | Outcome                                                                                       |
|--------------------------|-------------------------|------------------------|------------------------------|----------------------|-------------------------------------|-----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Shao et al. (2017) [27]  | Non-flavonoid polyphenols | Curcumin               | Anti-PD-L1 antibody (200 µg) | Bladder Cancer       | MB49 bladder carcinoma tumor-bearing C57BL/6 mice | - Increase intratumoral CD8+ T-cell infiltration  
- Elevated the level of IFN-γ in the blood  
- Decrease the number of intratumoral MDSCs | Prolonged survival of intraperitoneal metastasized bladder cancer |
| Dent et al. (2020) [28]  | Non-flavonoid polyphenols | Curcumin               | Anti-PD-1 antibody (50 mg/kg) | CRC                  | CT26 colorectal-tumor-bearing C57/BL6 mice | - Reduce the expression of PD-L1, PD-L2, and ODC  
- Elevated the level of MHCA | Reduce tumor growth |
| Guo et al. (2021) [29]   | Non-flavonoid polyphenols | Curcumin               | Anti-PD-1 antibody (10 mg/kg) | HCC                  | Hep3B hepatocellular tumor-bearing BALB/c female nude mice | - Reduce surface PD-L1 expression  
- Activate lymphocytes  
- Inhibit immune evasion  
- Down-regulate TGF-β1 expression | Lowered the HCC growth rate and improved tumor microenvironment |
| Gong et al. (2021) [30]  | Non-flavonoid polyphenols | Curcumin               | Anti-PD-1 antibody (10 mg/kg) | CRC                  | MC-38 colorectal-tumor-bearing C57BL/6 mice | N/A | - Reduce tumor growth and tumor volume  
- Reduce the risk of tumor recurrence (0% vs. 50% in the combination and IO monotherapy arms) |
| Hayakawa et al. (2021) [31] | Non-flavonoid polyphenols | Curcumin               | Anti-PD-1 Ab and Anti-PD-L1 Ab (200 µg/100 µL/mouse) | CRC                  | MC-38 colorectal-tumor-bearing C57BL/6 mice | Inhibit STAT3 expression induced by exogenous IL-6 | Reduce tumor growth |
| Liu et al. (2021) [32]   | Non-flavonoid polyphenols | Curcumin               | Anti-PD-L1 antibody (10 µg/mL) | HNSCC                | Human HNSCC cell lines (SNU1076, SNU1041, SCC15, and FaDu) | Reinvigorates defective T-cells through multiple (PD-1 and TIM-3) and multi-level (IC receptors and their ligands) IC axis inhibition | Reduce the tumor volume and weight |
| Kang et al. (2020) [33]  | Non-flavonoid polyphenols | Gallic acid            | Anti-PD-1 antibody (5 µg/mL) | NSCLC                | A549 and H292 NSCLC cell lines | - Reduce expression levels of PD-L1  
- Increase IFNγ levels | Decrease NSCLC cell viability |
| Lasso et al. (2020) [34] | Non-flavonoid polyphenols | Gallotannin           | Anti-PD-L1 antibody (200 µg) | Melanoma             | B16-F10 melanoma tumor-bearing C57BL/6 mice | - Increase IFNγ levels  
- Increase the number of activated CD4+ and CD8+ T-cells  
- Decrease the number of MDSCs  
- Increase PD-L1 expression | Decrease in tumor size |
## Table 1. Cont.

| Authors                  | Phytochemical Group | Phytochemical Compound | Immune Checkpoint Inhibitor | Cancer Type       | Cancer Model                        | Mechanism of Effect                                                                 | Outcome                                      |
|--------------------------|---------------------|------------------------|----------------------------|------------------|-------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------|
| Zhang et al. (2019) [35] | Non-flavonoid polyphenols | Resveratrol            | Anti-PD-L1 antibody (100 µg) | Ovarian Cancer   | Human ovarian carcinoma cell lines (SKOV3 and A2780) and murine ovarian carcinoma cell line (ID8) | Induction of tumor cell apoptosis           | Reduce tumor growth                         |
| Jiang et al. (2021) [25] | Flavonoid           | Luteolin Apigenin      | Anti-PD-1 antibody (10 mg/kg) | NSCLC            | KRAS-mutant human lung cell lines (H358, H460, H2122, and A549) and mice in vivo mode | Down-regulated the IFN-γ-induced PD-L1 expression by suppressing the phosphorylation of STAT3 | Reduce the tumor volume and weight         |
| Liu et al. (2020) [36]   | Flavonoid           | Bilberry Anthocyanin  | Anti-PD-L1 antibody (200 µg) | CRC              | MC-38 colorectal tumor-bearing C57BL/6 mice | Modulate the gut microbiome                                                           | Tumor growth delay                         |
| Mo et al. (2021) [37]    | Flavonoid           | Icaritin               | Anti-PD-1 antibody (10 mg/kg) | HCC, CRC, and melanoma | Human hepatocellular carcinoma, colorectal cancer and melanoma cell lines (HEPA1-6, MC-38, and B16F10) and mice in vivo model | Down-regulate PD-L1 expression and reduced nuclear translocation of NF-κB p6. | Reduce the tumor volume and weight         |
| Tang et al. (2019) [38]  | Flavonoid           | Melafolone             | Anti-PD-1 Ab (200 µg/100 µL/mouse) | Lung Cancer     | Lewis lung carcinoma or CMT tumor-bearing C57BL/6 mice | Down-regulate VEGF, TGF-β, and PD-L1 through COX-2 and EGFR inhibition | Promoted survival Tumor growth inhibition |
| Jiang et al. (2019) [39] | Terpenes            | Lycopene               | Anti-PD-1 antibody (6 mg/kg) | Lung Cancer      | Lewis lung carcinoma tumor-bearing C57BL/6 mice | - Increase IFNγ levels  
- Inhibit the expression of PD-L1 via activating JAK  
- Inhibit the phosphorylation of AKT | Reduce the tumor volume and weight         |
| Han et al. (2019) [40]   | Terpenes            | Cryptotanshinone       | Anti-PD-L1 antibody 10 µg   | HCC              | HCC-bearing mice model                | Develops long-term anti-tumor immunity and increased tumor infiltration of CD8+ T-cell | Tumor growth inhibition                     |
| Dong et al. (2018) [41]  | Terpenes            | Diosgenin              | Anti-PD-1 antibody (200 µg) | Melanoma         | B16-F10 melanoma tumor-bearing C57BL/6 mice | Enhances T-cell immune response by modulating intestinal microbiota and inducing T-cell infiltration | Tumor growth inhibition                     |
| Ye et al. (2021) [42]    | Others              | *Agrocybe aegerita* galectin | Anti-PD-1 Ab (200 µg intraperitoneal) | HCC              | H22, HepG2, and RAW264.7 cell lines Male Balb/c mice | Increase CD4+ and CD8+ T-cells with combination | Tumor growth inhibition                     |

Abbreviations: COX-2: Cyclooxygenase-2; EGFR: Epidermal growth factor receptor; HCC: Hepatocellular carcinoma; IFNy: Interferon-gamma; IL-6: Interleukin 6; MDSCs: Myeloid-derived suppressor cells; NSCLC: Non-small-cell lung carcinoma; MHCA: Human major histocompatibility complex class I A; PD-L: Programmed death ligand; ODC: Ornithine decarboxylase; STAT3: Signal transducer and activator of transcription 3; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.
4. Preclinical Studies Evaluating the Efficacy of Phytochemical and Immune Checkpoint Inhibitor Combinations

Several studies have evaluated the efficacy of ICI plus phytochemical combinations using variable phytochemicals in different cancer models (Table 2). The first report of a phytochemical and ICI combination strategy (bisdemethoxycurcumin with an anti-PD-L1 antibody) was published by Shao et al. in 2017 in a mouse bladder cancer model [27]. The researchers observed T-lymphocyte-based immune activation and removal of immune exhaustion via a decrease in the intratumoral myeloid-suppressor cells, leading to increased survival [27]. Later studies most frequently used curcumin, a non-flavonoid polyphenol, as the experimental phytochemical [28–31] and primarily focused on the colorectal cancer models [28,30,31,36], followed by NSCLC [33,38,39]. The intratumoral expansion of CD8+ or CD4+ lymphocytes and the increased levels of IFN-γ were consistent findings throughout the studies [34,42].

The decrease in PD-L1 levels was observed in five studies conducted with curcumin [28,29], lycopene [39], gallic acid [33], and melafolone [38] and could contribute to the synergism between ICI and phytochemicals by releasing the inhibitory breaks of immune checkpoints. In contrast, an increase in PD-L1 expression level was reported by Lasso et al. with gallatonin-rich Caesalpinia spinosa and anti-PD-L1 antibody combination [34]. The previous observations of PD-L1 expression increase with resveratrol and piceatannol in breast and colorectal cancer cell lines support the variable effects of different phytochemicals on immune checkpoint expressions [43], although the reason for contrasting effects on PD-L1 expression with the phytochemicals from the same class (non-flavonoid polyphenols) is yet to be defined.

While it could be problematic to expect a synergism between ICIs and phytochemicals, we think the differential effects of phytochemicals on PD-L1 expression levels could be beneficial to aid individualized treatment planning according to tumor microenvironments in different tumors. While decreasing immunosuppression secondary to decreased PD-L1 expression would be beneficial in a tumor-agnostic manner, increased ICI efficacy with increased tumoral PD-L1 expression levels was observed in NSCLC [33], melanoma [34], and bladder cancer [27] patients. Both the pretreatment with phytochemicals and the addition of phytochemicals at times of progression to increase PD-L1 expression should be evaluated as a treatment strategy, especially in tumors with an increased benefit with increased PD-L1 expressions.
Table 2. Summary of phytochemicals targeting PD-L1/PD-1 and CTLA-4 pathways in different types of cancer.

| Authors/Year          | Phytochemical Group | Phytochemical Compound | Source                                      | Cancer Type                   | Cancer Model or Toxicity                                      | Mechanism of Action                                                                 |
|-----------------------|---------------------|------------------------|---------------------------------------------|------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Liao et al. (2018)    | Non-flavonoid polyphenols | Curcumin              | Turmeric                                    | HNSCC                        | 4-NQO induced C57BL/6 tongue squamous cell carcinoma mice       | Decrease PD-L1 and p-STAT3\textsuperscript{705} protein expression                  |
| Deng et al. (2020)    | Non-flavonoid polyphenols | Curcumin              | Turmeric                                    | HCC                          | HepG2 hepatocellular tumor-bearing BALB/c female nude mice      | Decreased the protein expression of PD-L1 Inhibiting the TLR4/NF-\kappa B signaling pathway angiogenesis. |
| Lucas et al. (2018)   | Non-flavonoid polyphenols | Resveratrol            | Red wine, Grapes, Passion fruit             | Breast cancer                | Cal51 triple-negative breast cancer and SW620 colon cancer     | Increase the expression level of PD-L1 via HDAC3/p300-mediated nuclear factor (NF)-\kappa B signaling |
| Verdura et al. (2020) | Non-flavonoid polyphenols | Resveratrol            | Red wine, Grapes, Passion fruit             | Breast Cancer                | JIMT-1 and MDA-MB-231 breast cancer cells                      | Increased PD-L1 dysfunction                                                      |
| Yang et al. (2021)    | Non-flavonoid polyphenols | Resveratrol            | Red wine, Grapes, Passion fruit             | NSCLC                        | Human lung adenocarcinoma cell lines (A549 and H1299)          | Activation of SirT1 deacetylase leads to disassembly of the destruction complex, thereby enhancing the binding of \beta-catenin/TCF to the PD-L1 promoter |
| Coomb et al. (2016)   | Flavonoid            | Apigenin               | Parsley, onions, grapefruit, oranges,       | Breast Cancer                | Triple-negative MDA-MB-468 BC cells, HER2(+) SK-BR-3 BC cells, and 4T1 mouse mammary carcinoma cells | Inhibit IFN\gamma-induced PD-L1 upregulation                                       |
| Xu et al. (2018)      | Flavonoid            | Apigenin               | Apple, artichoke, basil, celery, cherry, grapes | Melanoma                     | B16-F10 melanoma tumor-bearing C57BL/6 mice                    | Inhibit the IFN-\gamma-induced activation of STAT Decreased expression levels of PD-L1 |
| Choi et al. (2020)    | Flavonoid            | Apigenin               | Salvia plebeia                              | CRC                          | hPD-L1 knock-in MC38 tumor-bearing humanized PD-1 mouse model   | Blocking of PD-1/PD-L1 interaction                                                 |
| Rawangkan et al.      | Flavonoid            | Epigallocatechin gallate (EGCG) | Green tea                                    | NSCLC                        | 4-(methylnitrosamo)-1-(3-pyridyl)-1- butanone induced nonsmall-cell lung cancer A/J mice | Down-regulate IFN-\gamma- and EGF-induced PD-L1 expression                          |
| Authors/Year              | Phytochemical Group | Phytochemical Compound | Source                  | Cancer Type          | Cancer Model or Toxicity                                      | Mechanism of Action                                                                 |
|--------------------------|---------------------|------------------------|-------------------------|----------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Sellam et al. (2020) [50] | Flavonoid           | Silibinin              | *Silibum marianum*      | HNSCC                | Nasopharyngeal carcinoma cell line                              | Down-regulation in PD-L1 expression by interfering with HIF-1α/LDH-A                  |
| Rugamba et al. (2021) [51]| Flavonoid           | Silibinin              | *Silibum marianum*      | NSCLC                | A549, H292, and H460 cell lines                                 | Suppresses the mRNA expression of PD-L1 and EMT regulators via inhibition of STAT3 phosphorylation |
| Wudtiwai et al. (2021) [52] | Flavonoid           | Hesperidin             | Orange peel and other citrus species | Oral Cancer | Human OSCC cell lines (HN6 and HN15)                             | Inhibition of phosphorylation of STAT1 and STAT3 down-regulates IFN-γ-induced PD-L1 expression |
| Ke et al. (2019) [24]     | Flavonoid           | Baicalin               | *Scutellaria baicalensis* | HCC                  | H22 hepatocellular tumor-bearing BALB/c mice or BALB/c-nu/nu mice | Decrease STAT3 activity Down-regulate IFN-γ-induced PD-L1 expression                  |
| Song et al. (2022) [53]   | Flavonoid           | Baicalin               | *Scutellaria baicalensis* | CRC                  | Human colon cancer cell lines (HCT-116 and CT26) and mice in vivo model | Inhibition of NF-κB signaling pathway down-regulated PD-L1 expression and MDSC, and up-regulated CD4 + and CD8 + T-cells |
| Liu et al. (2021) [54]    | Flavonoid           | Licochalcone A         | *Glycyrrhiza glabra*    | CRC                  | Human cancer cell lines (A549, HeLa, Hep3B, and HCT116) and mice in vivo model | PD-L1 expression was down-regulated by inhibition of NF-κB and Ras/Raf/MEK signaling pathways. |
| Hao et al. (2019) [55]    | Flavonoid           | Icaritin               | *Epimedium*             | Melanoma             | B16-F10 melanoma tumor-bearing C57BL/6 mice MC-38 colorectal tumor-bearing C57BL/6 mice | Reduce frequency of MDSCs Down-regulate PD-L1 expression                              |
| Mazewski et al. (2019) [56] | Flavonoid           | Cyanidin-3-O-glucoside | Blueberry, raspberry, black rice, cherry | CRC                  | Human colorectal cancer cell lines                               | Decreased PD-1 and PD-L1 protein expression                                           |
| Chen et al. (2022) [57]   | Flavonoid           | Myricetin              | Cranberry, blueberry, lemon, garlic | Lung cancer          | Human lung cancer cell lines (NCI-H1650, NCI-H460, and A549)     | Inhibition of IFN-γ-induced PD-L1 and IDO1 expression in cancer cells by inhibiting the JAK-STAT-IRF1 axis |
| Kim et al. (2020) [58]    | Flavonoid           | Kaempferol             | *Geraniı herba*         | N/A                  | PD-1 Jurkat and PD-L1/aAPC CHO-K1 cells                         | Inhibiting PD-1/PD-L1 Interaction                                                  |
Table 2. Cont.

| Authors/Year         | Phytochemical Group | Phytochemical Compound | Source               | Cancer Type | Cancer Model or Toxicity | Mechanism of Action                                                                 |
|----------------------|---------------------|------------------------|----------------------|-------------|--------------------------|-------------------------------------------------------------------------------------|
| Sahyon et al. (2020) [20] | Flavonoid           | Gallic acid            | Phoenix dactylifera  | N/A         | Adriamycin-induced cardiotoxicity and nephrotoxicity | Increased cardiac and kidney PD-1 protein percentage                                    |
| Xing et al. (2018) [22] | Terpenes            | Fraxinellone           | Dictamnus dasycarpus | Lung cancer | Human A549 lung cancer cell line | Inhibit PD-L1 expression by downregulating the STAT3 and HIF-1α signaling pathways |
| Huang et al. (2019) [39] | Terpenes            | Platycodin             | Platycodon grandiflorus | Lung cancer | NCI-H1975 and NCI-H358 lung cancer cell lines | Down-regulate the protein level of PD-L1                                               |
| Zhang et al. (2019) [60] | Terpenes            | Triptolide             | Tripterygium wilfordii | Glioma      | Glioma cells              | Down-regulated IFN-γ-induced PD-L1 expression                                         |
| Kuo et al. (2021) [61] | Terpenes            | Triptolide             | Tripterygium wilfordii | HNSCC       | OSCC cell line SAS (JCRB0260) and mice in vivo model | Reduces IFN-γ-related JAK2-STAT1 pathway and decreases PD-L1 expression               |
| Tian et al. (2021) [17] | Phytosterol         | Z-guggulsterone        | Commiphora mukul tree | NSCLC       | Lewis lung carcinoma tumor-bearing C57BL/6 mice | Inducing PD-L1 upregulation partly mediated by FXR, Akt, and Erk1/2 signaling pathways |
| Wang et al. (2020) [62] | Saponins            | Panaxadiol             | Panax ginseng        | CRC         | HCT116, SW620, HT29, and HEK293 colon cancer cell line and mice in vivo model | Reduces PD-L1 expression by suppressing HIF-1α and STAT3                               |
| Deng et al. (2020) [44] | Saponins            | Ginsenosides           | Panax                | HCC         | HepG2 hepatocellular tumor-bearing BALB/c female nude mice | Decreased the protein expression of PD-L1 inhibiting the TLR4/NF-κB signaling pathway angiogenesis. |
| Bedi et al. (2019) [63] | Alkaloid            | Camptothecin           | Camptotheca acuminata | CRC         | SW620, HCT116, and RKO colon cancer cells | Reduces PD-L1 expression and upregulates the secretion of pro-tumorigenic cytokines |
| Hunakova et al. (2019) [64] | Isothiocyanates     | Isothiocyanate         | Broccoli, Brussels sprouts, cabbage, cauliflower, horseradish | Breast Cancer | Human triple-negative Breast Carcinoma MDA-MB-231 Cells | Decrease expression levels of PD-L1                                                    |
| Chang et al. (2019) [65] | Astragalus membranaceous extract | Extract              | Astragalus membranaceous | Breast cancer, CRC | Mouse breast cancer 4T1 and colorectal cancer CT26 | Down-regulate PD-L1 expression by suppressing the AKT signaling pathway |
| Authors/Year                  | Phytochemical Group | Phytochemical Compound | Source                              | Cancer Type          | Cancer Model or Toxicity | Mechanism of Action                                                                 |
|------------------------------|---------------------|------------------------|-------------------------------------|----------------------|-------------------------|------------------------------------------------------------------------------------|
| Li et al. (2019) [16]        | *Rhus verniciflua*  | Eriodictyol, fisetin, quercetin, liquiritigenin | *Rhus verniciflua* Stokes          | N/A                  |                         | Blocked both the PD-1/PD-L1 and the CTLA-4/CD80 interactions                        |
| Safonova et al. (2020) [66]  | *Tussilago farfara* | Rhamnogalacturonan I and neutral polysaccharides complex | *Tussilago farfara*               | Lung cancer          | Lewis lung carcinoma tumor-bearing C57BL/6 mice                                     | Reducing expression levels of PD-1 and PD-L1 Interaction                            |
| Ryan et al. (2022) [67]      | *Black raspberry*   | Extract                | *Black raspberry*                   | HNSCC                | Nitroquinoline-1-oxide (4NQO) induced head and neck cancer C57BL/6 mice            | Decreased levels of PD-L1 expression                                               |

Abbreviations: 4-NQO: 4-nitroquinoline-1-oxide; CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4; EGF: Epidermal growth factor; ERK1/2: Extracellular signal-regulated kinase 1/2; FXR: farnesoid X receptor; HIF-1: hypoxia-inducible factor-1; HNSCC: Head and neck squamous cell carcinoma; IFNγ: Interferon-gamma; LDH: Lactate dehydrogenase; MDSCs: Myeloid-derived suppressor cells; NSCLC: Non-small-cell lung carcinoma; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PD-L: Programmed death ligand; STAT3: Signal transducer and activator of transcription.
5. Clues from Microbiome Studies on the Benefit of Phytochemicals in Immunotherapy Efficacy

The commensal bacteria residing in the gastrointestinal system and their genome is called the gastrointestinal (GI) microbiome. The GI microbiome plays significant roles in self-defense and inflammation [68]. Recently, the GI microbiome has emerged as a predictor of ICI efficacy, and several studies have demonstrated better survival in ICI-treated patients enriched with beneficial commensal bacteria, including *Akkermansia muciniphila*, *Bacteroides* spp., and *Faecalibacterium prausnitzii*. *Akkermansia muciniphila* in particular was associated with a response to ICIs in four studies conducted on patients with three different tumors (RCC, NSCLC, and HCC) [69–72]. Whether the increases in these bacteria are secondary to a bystander effect or these bacteria play roles in ICI efficacy is highly debated. However, the restoration of ICI efficacy with *Akkermansia muciniphila* transplantation in ICI non-responders mice [70] and the recent report of improved ICI efficacy with microbiome and ICI combination in metastatic renal cell carcinoma patients [73] point to an anti-tumor role of the microbiome rather than it only being a biomarker.

Several phytochemicals such as curcumin and phenols could increase levels of beneficial commensal bacteria (Table 3) and correct the dysbiosis created by oxidative stress, as shown in alcoholic liver disease and fatty liver disease models. Similarly, phytochemicals could correct dysbiosis in patients treated with ICIs. These phytochemicals are most commonly found in fiber-rich diets (Table 3). Frankel et al. reported indirect evidence of this strategy’s possible benefit in melanoma patients [14]. Metabolomic analyses in 39 ICI-treated melanoma patients revealed that the anacardic acid levels were increased in responders. Most of these patients (five out of six) had dietary habits that explained the high anacardic acid levels. Based on these points, we think using phytochemicals to correct dysbiosis and increase levels of bacteria associated with ICI efficacy should be exploited in clinical trials. Additionally, further research is needed to delineate the optimal fiber type to consume for ICI efficacy. Recently, Nakajima et al. reported that a soluble fiber diet increased gut *Bacteroides fragilis*, previously associated with ICI response, while the insoluble fiber-rich diet reduced the *Bacteroides fragilis* levels in a mice model [74]. In addition, Li et al. previously demonstrated the enrichment of beneficial commensal Actinobacteria and Akkermansia in obese mice fed with nondigestible fructans, which are found in higher concentrations in bananas, compared to mice fed with cellulose [75,76]. Until the results of these trials become available, the recommendation of eating soluble fiber-rich diets and diets rich in phytochemicals that increase beneficial commensal bacteria could benefit ICI-treated patients.
Table 3. Summary of phytochemicals as modifiers of the gut microbiome in the immunotherapy studies (adapted from Guven DC et al. [77]).

| Lead Author, Year | Target Population/Patient Number (n) | Main Findings | Candidate Phytochemical Nutrient | Phytochemical Enriched Nutrient | Bacteria |
|-------------------|--------------------------------------|----------------|----------------------------------|---------------------------------|----------|
| Vetizou et al. (2015) [78] | Melanoma/25 | Increased levels of *Bacteroides thetaiotaomicron* and *Bacteroides fragilis* in ICI responders Improved response to CTLA-4 blockade with FMT from patients with increased fecal *Bacteroides* spp. levels | Polyphenol/coumarin [79] | Soluble fiber-rich diet [74]/High coffee-consumption [80] | *Bacteroides thetaiotaomicron* *Bacteroides fragilis* |
| Sivan et al. (2015) [81] | Melanoma/Mice | Increased levels of *Bacteroides* spp. in ICI responders Similar tumor control as PD-L1 blockade with oral supplementation of *Bifidobacterium* spp. | Resveratrol [82] | Grapes, wine, and peanuts [83] | *Bifidobacterium* spp. |
| Dubin et al. (2016) [84] | Melanoma/34 | Lower risk of colitis in *Bacteroides* spp. enriched patients | Polyphenol/coumarin [79] | Soluble fiber-rich diet [74]/High coffee-consumption [80] | *Bacteroides* spp. |
| Chaput et al. (2017) [85] | Melanoma/26 | Longer progression-free and overall survival in *Faecalibacterium* spp. enriched patients | Anthocyanin [86] | Black Raspberries [86] | *Faecalibacterium* spp. |
| Gopalakrishnan et al. (2018) [87] | Melanoma/112 | Higher alpha diversity and increased *Ruminococcaceae* levels in the feces of ICI responders Higher buccal and fecal levels of *Bacteroidales* in ICI non-responders | Polyphenols [88] (Naringenin and quercetin) Anthocyanin [89] | Onion, apple, broccoli [90] Black Raspberries [89] | *Ruminococcaceae* *Bacteroidales* |
| Matson et al. (2018) [91] | Melanoma/42 | Increased *Bifidobacterium longum* in the feces of ICI responders Tumor control, augmented T-cell responses, and improved efficacy of anti-PD-L1 blockade with oral supplementation of responders’ feces to germ-free mice | Resveratrol [92] | Grapes, wine, and peanuts [83] | *Bifidobacterium longum* |
| Routy et al. (2018) [69] | NSCLC/140 RCC/67 | Increased levels of *Akkermansia muciniphila* in ICI responders Restoration of the efficacy of PD-1 blockade in antibiotic pretreated mice after FMT from ICI responders | Curcumin [93]/EGCG [94] | Prebiotic nondigestible fiber-rich diet [95] | *Akkermansia muciniphila* |
| Lead Author, Year | Target Population/Patient Number (n) | Main Findings | Candidate Phytochemical Phytochemical Enriched Nutrient | Bacteria |
|-------------------|--------------------------------------|---------------|--------------------------------------------------------|----------|
| Peters et al. (2018) [96] | Melanoma/26 | Lower risk of progression in patients with higher community diversity Lower risk of progression in patients enriched with Faecalibacterium prausnitzii | Anthocyanin [86] | Black Raspberries [86] Faecalibacterium prausnitzii |
| Fukuoka et al. (2018) [97] | NSCLC/14 Gastric cancer/24 | Higher alpha diversity and Ruminococcaceae levels in ICI responders | Ellagitannins [98] | Pomegranates, nuts [99] Ruminococcaceae |
| Derosa et al. (2018) [70] | RCC/85 | Increased abundance of Akkermansia muciniphila and Bacteroides salyersiae in non-resistant renal cell carcinoma patients Restoration of the efficacy of the ICI with Akkermansia muciniphila and Bacteroides salyersiae transplantation to mice with unfavorable/dysbiotic profile | Curcumin [93]/EGCG [94] Prebiotic nondigestible fiber-rich diet [95] | Not reported Bacteroides salyersiae |
| Maia et al. (2018) [100] | RCC/20 | Increased abundance of Roseburia and Faecalibacterium spp. in ICI responders | Anthocyanin [86] Polyphenols [101] | Black Raspberries [86] Resistant Starch [101] Faecalibacterium prausnitzii Roseburia |
| Botticelli et al. (2020) [102] | NSCLC/11 | Increased fecal Akkermansia muciniphila, Bifidobacterium longum, and Faecalibacterium prausnitzii levels in ICI responders | Curcumin [93]/EGCG [94] Resveratrol [82], Anthocyanin [103] Anthocyanin [86] | Prebiotic nondigestible fiber-rich diet [95] Grapes, wine, and peanuts [83], Chinese purple sweet potato cultivar [103], Black Raspberries [86] Akkermansia muciniphila Bifidobacterium longum Faecalibacterium prausnitzii |
| Liu et al. (2020) [36] | CRC/mice | The addition of anthocyanins in the α-PD-L1 treatment showed an overrepresentation of Lachnospiraceae and Ruminococcaceae | Anthocyanin [86] | Black Raspberries [86] Ruminococcaceae and Lachnospiraceae |
| Chung et al. (2021) [71] | HCC/8 | Increased fecal Akkermansia levels in ICI responders | Curcumin [93]/EGCG [94] | Prebiotic nondigestible fiber-rich diet [95] Grapes, wine, and peanuts [83] Akkermansiaceae |
| Grenda et al. (2022) [72] | NSCLC/47 | Increased fecal Akkermansia levels in ICI responders | Curcumin [93]/EGCG [94] | Prebiotic nondigestible fiber-rich diet [95] Grapes, wine, and peanuts [83] Akkermansiaceae |

Abbreviations: EGCG: Epigallocatechin gallate; FMT: Fecal microbiota transfer; ICI: Immune checkpoint inhibitors; NSCLC: Non-small-cell lung carcinoma; RCC: Renal cell carcinoma.
6. Future Perspectives

Phytochemicals have several effects on promoting anti-tumor immunity and modulating the tumor microenvironment, including immune checkpoints. Based on the available preclinical evidence, phytochemicals have the potential to transform immunologically cold tumors into hot tumors and improve immunotherapy efficacy. This strategy could be especially promising for tumors that have consistently garnered less benefit from ICIs, including sarcomas and brain tumors [104,105]. The available preclinical evidence and the demonstration of higher ICI response rates in melanoma patients with increased anacardic acid levels in metabolomic studies support the progression of phytochemical and ICI combinations to clinical studies [14]. Patient-derived xenograft models would be suitable venues to assess the clinical use of phytochemicals in transforming tumor immune profiles and would be beneficial for further clinical studies.

Combining chemotherapy and ICIs and combining two ICIs (CTLA-4 and PD-1/PD-L1) has become the standard of care in the first-line treatment of NSCLC, gastric cancer, RCC, and melanoma, with improved response rates and survival [106–110]. The increased immune activation in the tumor microenvironment was among the main drivers of the increased efficacy of these combinations [111]. However, the efficacy of adding phytochemicals to these combinations has not been investigated yet. We think that phytochemicals could add benefits to these combinations, and further research focusing on the efficacy of adding phytochemicals to chemotherapy-ICI and ICI-ICI combinations could have implications for current clinical practice.

Another knowledge gap concerns the efficacy of using phytochemical and ICI combinations in adjuvant settings. Although it would be harder to measure the efficacy of phytochemical and ICI combinations in adjuvant settings, animal models with radiated tumors or chemoprevention models using ICI and phytochemical combinations should be designed considering the well-known efficacy of phytochemicals in chemoprevention.

Lastly, the phytochemical structure of the traditional herbs with well-known immunomodulatory effects should be thoroughly delineated to identify more candidates to combine with ICIs. For example, Artemisia products are used in China to fight malaria, allergies, and auto-immune diseases [112]. The recently conducted phytochemical analysis of Artemisia annua L. demonstrated the presence of several flavonoids, hydroxycoumarins, and phytosterols, phytochemicals with possible anticancer effects on immune checkpoints [113]. Furthermore, recent gene expression analyses in HCC about Artemisia scoparia demonstrated the increased expression of BIRC5 and secondary expression of CTLA-4 and LAG-3 immune checkpoints and a possible immune activation with this herbal medicine [114]. Further studies evaluating the phytochemical constituent of herbal medications and corresponding effects on the immune checkpoints are needed.

7. Conclusions

In conclusion, plant-based phytochemicals could be beneficial adjuncts to ICIs with improved immune activation and tumor microenvironment modulation. Further research is needed considering the difficult scenarios in the clinical practice and the areas needing improvement to answer more clinically oriented questions.

Author Contributions: D.C.G. and K.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: D.C.G., A.R., A.D.R., S.A. and K.S. Data collection: D.C.G., T.K.S., A.R. and A.D.R. Statistical analysis: D.C.G., T.K.S., A.R., A.D.R., S.A. and K.S. Drafting of the manuscript: D.C.G. and K.S. Critical revision of the manuscript for important intellectual content: D.C.G., T.K.S., A.R., A.D.R., S.A. and K.S. Study supervision: D.C.G., A.R., A.D.R., S.A. and K.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.
25. Jiang, Z.B.; Wang, W.J.; Xu, C.; Xie, Y.J.; Wang, X.R.; Zhang, Y.Z.; Huang, J.M.; Huang, M.; Xie, C.; Liu, P.; et al. Luteolin and its derivative apigenin suppress the inducible PD-L1 expression to improve anti-tumor immunity in KRAS-mutant lung cancer. *Cancer Lett.* 2021, 515, 36–48. [CrossRef]

26. Avalle, L.; Pensà, S.; Regis, G.; Novelli, F.; Poli, V. STAT1 and STAT3 in tumorigenesis: A matter of balance. *JAK-STAT* 2022, 1, 65–72. [CrossRef] [PubMed]

27. Shao, Y.; Zhu, W.; Da, J.; Xu, M.; Wang, Y.; Zhou, J.; Wang, Z. Bisdemethoxycurcumin in combination with α-PD-L1 antibody boosts immune response against bladder cancer. *Onco Targets Ther.* 2017, 10, 2675–2683. [CrossRef]

28. Dent, P.; Booth, L.; Roberts, J.L.; Poklepovic, A.; Hancock, J.F. (Curcumin+sildenafil) enhances the efficacy of 5FU and anti-PD1 therapies in vivo. *J. Cell. Physiol.* 2020, 235, 6862–6874. [CrossRef] [PubMed]

29. Guo, L.; Li, H.; Fan, T.; Ma, Y.; Wang, L. Synergistic efficacy of curcumin and anti-programmed cell death-1 in hepatocellular carcinoma. *Life Sci.* 2021, 279, 119359. [CrossRef]

30. Gong, F.; Ma, J.-C.; Jia, J.; Li, F.-Z.; Wu, J.-L.; Wang, S.; Teng, X.; Cui, Z.-K. Synergistic effect of the anti-PD-1 antibody with blood stable and reduction sensitive curcumin micelles on colon cancer. *Drug Deliv.* 2021, 28, 930–942. [CrossRef]

31. Hayakawa, T.; Yaguchi, T.; Kawakami, Y. Enhanced anti-tumor effects of the PD-1 blockade combined with a highly absorptive form of curcumin targeting STAT3. *Cancer Sci.* 2020, 111, 4326–4335. [CrossRef]

32. Liu, L.; Lim, M.A.; Jung, S.-N.; Oh, C.; Won, H.-R.; Jin, Y.L.; Piao, Y.; Kim, H.J.; Chang, J.W.; Koo, B.S. The effect of Curcumin on multi-level immune checkpoint blockade and T cell dysfunction in head and neck cancer. *Phytotherapy* 2021, 92, 153758. [CrossRef]

33. Kang, D.Y.; Sp, N.; Jo, E.S.; Rugamba, A.; Hong, D.Y.; Lee, H.G.; Yoo, J.S.; Liu, Q.; Jang, J.K.; Yang, Y.M. The Inhibitory Mechanisms of Tumor PD-L1 Expression by Natural Bioactive Gallic Acid in Non-Small-Cell Lung Cancer (NSCLC) Cells. *Cancers* 2020, 12, 727. [CrossRef]

34. Lasso, P.; Gomez-Cadena, A.; Urueña, C.; Donda, A.; Martinez-Usatorre, A.; Romero, P.; Barreto, A.; Fiorentino, S. An Immunomodulatory Gallotannin-Rich Fraction From Caesalpinia spinosa Enhances the Therapeutic Effect of Anti-PD-L1 in Melanoma. *Front. Immunol.* 2020, 11, 584995. [CrossRef]

35. Zhang, Y.; Yang, S.; Yang, Y.; Liu, T. Resveratrol induces immunogenic cell death of human and murine ovarian carcinoma cells. *Infect. Agent Cancer* 2019, 14, 27. [CrossRef]

36. Liu, X.; Wang, L.; Jing, N.; Jiang, G.; Liu, Z. Biostimulating Gut Microbiome with Bilberry Anthocyanin Combo to Enhance Anti-PD-L1 Efficiency against Murine Colorectal Cancer. *Microorganisms* 2020, 8, 175. [CrossRef] [PubMed]

37. Mo, D.; Zhu, H.; Wang, J.; Hao, H.; Guo, Y.; Wang, J.; Han, X.; Zou, L.; Li, Z.; Yao, H.; et al. Icaritin inhibits PD-L1 expression by Targeting Protein IκB Kinase α. *Eur. J. Immunol.* 2021, 51, 978–988. [CrossRef] [PubMed]

38. Tang, H.; Liu, Y.; Wang, C.; Zheng, H.; Chen, Y.; Liu, W.; Chen, X.; Zhang, J.; Chen, H.; Yang, Y.; et al. Inhibition of COX-2 and EGFR by Melafolone Improves Anti-PD-1 Therapy through Vascular Normalization and PD-L1 Downregulation in Lung Cancer. *J. Pharmaco. Exp. Ther.* 2019, 368, 401–413. [CrossRef] [PubMed]

39. Jiang, X.; Wu, H.; Zhao, W.; Ding, X.; You, Q.; Zhu, F.; Qian, M.; Yu, P. Lycopene improves the efficiency of anti-PD-1 therapy via activating IFN signaling of lung cancer cells. *Cancer Cell Int.* 2019, 19, 68. [CrossRef]

40. Han, Z.; Liu, S.; Lin, H.; Trivet, A.L.; Hannifin, S.; Yang, D.; Oppenheim, J.J. Inhibition of murine hepatoma tumor growth by cryptotanshinone involves TLR7-dependent activation of macrophages and induction of adaptive anti-tumor immune defenses. *Cancer Immunol. Immunother.* 2020, 69, 1073–1085. [CrossRef]

41. Dong, M.; Meng, Z.; Kuerban, K.; Qi, F.; Liu, J.; Wei, Y.; Wang, Q.; Jiang, S.; Feng, M.; Ye, L. Diosgenin promotes antitumor immunity and PD-1 antibody efficacy against melanoma by regulating intestinal microbiota. *Cell Death Dis.* 2018, 9, 1039. [CrossRef]

42. Ye, X.; Wang, X.; Yu, W.; Yang, Q.; Li, Y.; Jin, Y.; Su, Y.; Song, J.; Xu, B.; Sun, H. Synergistic effects of AAGL and anti-PD-1 on hepatocellular carcinoma through lymphocyte recruitment to the liver. *Cancer Biol. Med.* 2021, 18, 1092. [CrossRef] [PubMed]

43. Lucas, J.; Hsieh, T.C.; Halicka, H.D.; Darzynkiewicz, Z.; Wu, J.M. Upregulation of PD-L1 expression by resveratrol and piceatannol in breast and colorectal cancer cells occurs via HDAC3/p300-mediated NF-κB signaling. *Int. J. Oncol.* 2018, 53, 1469–1480. [CrossRef] [PubMed]

44. Deng, Z.; Xu, X-Y.; Yunita, F.; Zhou, Q.; Wu, Y-R.; Hu, Y-X.; Wang, Z-Q.; Tian, X-F. Synergistic anti-liver cancer effects of curcumin and total ginsenosides. *World J. Gastrointest. Oncol.* 2020, 12, 1091–1103. [CrossRef]

45. Verdura, S.; Cuyas, E.; Cortada, E.; Brunet, J.; Lopez-Bonet, E.; Martin-Castillo, B.; Bosch-Barrera, J.; Encinar, J.A.; Menendez, J.A. Resveratrol targets PD-L1 glycosylation and dimerization to enhance anti-tumor T-cell immunity. *Aging* 2020, 12, 8. [CrossRef] [PubMed]

46. Yang, M.; Li, Z.; Tao, J.; Hu, H.; Li, Z.; Zhang, Z.; Cheng, F.; Sun, Y.; Zhang, Y.; Yang, J.; et al. Resveratrol induces PD-L1 expression through snail-driven activation of Wnt pathway in lung cancer cells. *J. Cancer Res. Clin. Oncol.* 2021, 147, 1101–1113. [CrossRef] [PubMed]

47. Coombs, M.R.P.; Harrison, M.E.; Hoskin, D.W. Apigenin inhibits the inducible expression of programmed death ligand 1 by human and mouse mammary carcinoma cells. *Cancer Lett.* 2016, 380, 424–433. [CrossRef]

48. Choi, J.-G.; Kim, Y.S.; Kim, J.H.; Kim, T.I.; Li, W.; Oh, T.W.; Jeon, C.H.; Kim, S.J.; Chung, H.-S. Anticancer Effect of Salvia plebeia and Its Active Compound by Improving T-Cell Activity via Blockade of PD-1/PD-L1 Interaction in Humanized PD-1 Mouse Model. *Front. Immunol.* 2020, 11, 8556. [CrossRef]
49. Rawangkan, A.; Wongwirathan, P.; Namiki, K.; Iida, K.; Kobayashi, Y.; Shimizu, Y.; Fujiki, H.; Sugaruma, M. Green Tea Extract is an Alternative Immune Checkpoint Inhibitor that Inhibits PD-L1 Expression and Lung Tumor Growth. *Molecules* 2018, 23, 2071. [CrossRef]

50. Sellam, L.S.; Zappasodi, R.; Chettab, F.; Djennou, D.; Yahi-Ait Mesbah, N.; Amir-Tidadi, Z.C.; Touil-Boukoffa, C.; Ouahione, W.; Merghouth, T.; Bourouba, M. Silibinin down-regulates PD-L1 expression in nasopharyngeal carcinoma by interfering with tumor cell glycolytic metabolism. *Arch. Biochem. Biophys.* 2020, 690, 108479. [CrossRef]

51. Rugamba, A.; Kang, D.Y.; Sp. N.; Jo, E.S.; Lee, J.M.; Bae, S.W.; Jang, K.J. Silibinin Regulates Tumor Progression and Tumorsphere Formation by Suppressing PD-L1 Expression in Non-Small Cell Lung Cancer (NSCLC) Cells. *Cells* 2021, 10, 1632. [CrossRef]

52. Wudtiwai, B.; Makeudom, A.; Krissanaprakornkit, S.; Poithachatarn, P.; Kongtawelert, P. Anticancer Activities of Hesperidin via Suppression of Up-Regulated Programmed Death-Ligand 1 Expression in Oral Cancer Cells. *Molecules* 2021, 26, 5345. [CrossRef] [PubMed]

53. Song, L.; Zhu, S.; Liu, C.; Zhang, Q.; Liang, X. Baicalin triggers apoptosis, inhibits migration, and enhances anti-tumor immunity in colorectal cancer via TLR4/NF-κB signaling pathway. *J. Food Biochem.* 2022, 46, e13703. [CrossRef] [PubMed]

54. Liu, X.; Xing, Y.; Li, M.; Zhang, Z.; Wang, J.; Ri, M.; Jin, C.; Xu, G.; Piao, L.; Jin, H.; et al. Licochalcone A inhibits proliferation and promotes apoptosis of colon cancer cell by targeting programmed cell death-ligand 1 via the NF-κB and Ras/Raf/MEK pathways. *J. Ethnopharmacol.* 2021, 273, 113989. [CrossRef]

55. Mazewski, C.; Kim, M.S.; Gonzalez de Mejia, E. Anthocyanins, delphinidin-3-O-glucoside and cyanidin-3-O-glucoside, inhibit immune checkpoints in human colorectal cancer cells in vitro and in silico. *Sci. Rep.* 2019, 9, 11560. [CrossRef]

56. Chen, Y.-C.; He, X.-L.; Shi, W.; Yuan, L.-W.; Huang, M.-Y.; Xu, Y.-L.; Chen, X.; Gu, L.; Zhang, L.-L.; et al. Myricetin inhibits interferon-γ-induced PD-L1 and IDO1 expression in lung cancer cells. *Biochem. Pharmacol.* 2022, 197, 114940. [CrossRef] [PubMed]

57. Kim, J.H.; Kim, Y.S.; Choi, J.-G.; Li, W.; Lee, E.J.; Park, J.-W.; Song, J.; Chung, H.-S. Kaempferol and Its Glycoside, Kaempferol 7-O-Rhamnoside, Inhibit PD-1/PD-L1 Interaction In Vitro. *Int. J. Mol. Sci.* 2020, 21, 3239. [CrossRef]

58. Huang, M.-Y.; Jiang, X.-M.; Xu, Y.-L.; Yuan, L.-W.; Chen, Y.-C.; Cui, G.; Huang, R.-Y.; Liu, B.; Wang, Y.; Chen, X.; et al. Platycodin D triggers the extracellular release of programmed death Ligand-1 in lung cancer cells. *Food Chem. Toxicol.* 2019, 131, 110537. [CrossRef] [PubMed]

59. Zeng, L.; Yu, J.S. Triptolide reverses helper T cell inhibition and down-regulates IFN-γ induced PD-L1 expression in glioma cell lines. *J. Neurooncol.* 2019, 143, 429–436. [CrossRef] [PubMed]

60. Kuo, C.S.; Yang, C.Y.; Lin, C.K.; Lin, G.J.; Sytwu, H.K.; Chen, Y.W. Triptolide suppresses oral cancer cell PD-L1 expression in the interferon-γ-modulated microenvironment in vitro, in vivo, and in clinical patients. *Biomed. Pharm.* 2021, 133, 110857. [CrossRef] [PubMed]

61. Wang, Z.; Li, M.Y.; Zhang, Z.H.; Zuo, H.X.; Wang, J.Y.; Xing, Y.; Ri, M.; Jin, H.L.; Jin, C.H.; Xu, G.H.; et al. Panaxadiol inhibits programmed cell death-ligand 1 expression and tumour proliferation via hypoxia-inducible factor (HIF)-1α and STAT3 in human colon cancer cells. *Pharm. Res.* 2020, 155, 104727. [CrossRef] [PubMed]

62. Bedi, D.; Henderson, H.J.; Manne, U.; Samuel, T. Camptothecin Is an Alternative Immune Checkpoint Inhibitor that Inhibits PD-L1 Expression and Lung Tumor Growth. *Molecules* 2020, 25, 4975. [CrossRef] [PubMed]

63. Safonova, E.A.; Lopatina, K.A.; Razina, T.G.; Zueva, E.P.; Gur’ev, A.M.; Belousov, M.V. Effects of Tussilago farfara L. Polysaccharides on the Expression of PD-1 (CD279) and PD-L1 (CD274) in Peripheral Blood and Tumor Tissue Lymphocytes in Mice with Lewis Lung Carcinoma. *Bull. Exp. Biol. Med.* 2020, 169, 378–382. [CrossRef]

64. Ryan, N.M.; Lamenza, F.F.; Upadhaya, P.; Pracha, H.; Springer, A.; Swingle, M.; Siddiqui, A.; Oghumu, S. Black raspberry extract inhibits regulatory T-cell activity in a murine model of head and neck squamous cell carcinoma chemoprevention. *Front. Immunol.* 2022, 13, 2742. [CrossRef]

65. Wu, H.-J.; Wu, E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012, 3, 4–14. [CrossRef] [PubMed]

66. Routy, B.; Le Chateelier, E.; Derosa, L.; Duong, C.P.M.; Alou, M.T.; Daillere, R.; Fluckiger, A.; Messaoudene, M.; Rauber, C.; Roberti, M.P.; et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018, 359, 91–97. [CrossRef] [PubMed]

67. Derosa, L.; Iebba, V.; Albiges, L.; Fidelle, M.; Bonvalet, M.; Colomba, E.; Zitvogel, L.; Escudier, B.; Routy, B. Gut microbiome composition to predict resistance in renal cell carcinoma (RCC) patients on nivolumab. *J. Clin. Oncol.* 2018, 36, 4519. [CrossRef]
71. Chung, M.W.; Kim, M.J.; Won, E.J.; Lee, Y.J.; Yun, Y.W.; Cho, S.B.; Joo, Y.E.; Hwang, J.E.; Bae, W.K.; Chung, I.J.; et al. Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients. *World J. Gastroenterol.* 2021, 27, 7340–7349. [CrossRef]

72. Grenda, A.; Iwan, E.; Chmielewska, I.; Krawczyk, P.; Giza, A.; Bomba, A.; Frak, M.; Rolska, A.; Szczurek, M.; Kieszko, R.; et al. Presence of Akkermansia muciniphila in gut microbiome and immunotherapy effectiveness in patients with advanced non-small cell lung cancer. *AMB Express* 2022, 12, 86. [CrossRef] [PubMed]

73. Dizman, N.; Meza, L.; Bergerot, P.; Alcantara, M.; Dorff, T.; Lyou, Y.; Frankel, P.; Cui, Y.; Mira, V.; Llamas, M.; et al. Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: A randomized phase 1 trial. *Nat. Med.* 2022, 28, 704–712. [CrossRef]

74. Nakajima, A.; Sasaki, T.; Itoh, K.; Kitahara, T.; Takema, Y.; Hiramatsu, K.; Ishikawa, D.; Shibuya, T.; Kobayashi, O.; Osada, T.; et al. A Soluble Fiber Diet Increases *Bacteroides fragilis* Group Abundance and Immunoglobulin A Production in the Gut. *Appl. Environ. Microbiol.* 2020, 86, e00405-20. [CrossRef] [PubMed]

75. Liu, T.-W.; Cephas, K.D.; Holischer, H.D.; Kerr, K.R.; Mangian, H.F.; Tappenden, K.A.; Swanson, K.S. Nondigestible Fructans Alter Gastrointestinal Barrier Function, Gene Expression, Histomorphology, and the Microbiota Profiles of Diet-Induced Obese C57BL/6J Mice. *J. Nutr.* 2016, 146, 949–956. [CrossRef] [PubMed]

76. Shalini, R.; Abinaya, G.; Saranya, P.; Antony, U. Growth of selected probiotic bacterial strains with fructans from Nendran banana and garlic. *JWT Food Sci. Technol.* 2017, 83, 68–78. [CrossRef]

77. Guven, D.C.; Aktas, B.Y.; Simsek, A.; Aksoy, S. Gut microbiota and cancer immunotherapy: Prognostic and therapeutic implications. *Future Oncol.* 2020, 16, 497–506. [CrossRef]

78. Vézizou, M.; Pitt, J.M.; Daillère, R.; Lepage, P.; Waldschmitt, N.; Flamet, C.; Rusakiewicz, S.; Routy, B.; Roberti, M.P.; Duong, C.P.; et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015, 350, 1079–1084. [CrossRef] [PubMed]

79. Zhang, C.; Wu, W.; Li, X.; Xin, X.; Liu, D. Daily Supplementation with Fresh Angelica keiskei Juice Alleviates High-Fat Diet-Induced Obesity in Mice by Modulating Gut Microbiota Composition. *Mol. Nutr. Food Res.* 2019, 63, e1900248. [CrossRef]

80. González, S.; Salazar, N.; Ruiz-Saavedra, S.; Gómez-Martin, M.; de Los Reyes-Gavilán, C.G.; Gueimonde, M. Long-Term Coffee Consumption is Associated with Fecal Microbial Composition in Humans. *Nutrients* 2020, 12, 1287. [CrossRef]

81. Sivan, A.; Corrales, L.; Hubert, N.; Williams, J.B.; Aquino-Michaels, K.; Earley, Z.M.; Benyamin, F.W.; Lei, Y.M.; Jabri, B.; Alegre, M.L.; et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015, 350, 1084–1089. [CrossRef] [PubMed]

82. Qiao, Y.; Sun, J.; Xia, S.; Tang, X.; Shi, Y.; Le, G. Effects of resveratrol on gut microbiota and fat storage in a mouse model with high-fat-induced obesity. *Food Funct.* 2014, 5, 1241–1249. [CrossRef] [PubMed]

83. Burns, J.; Yokota, T.; Ashihara, H.; Lean, M.E.J.; Crozier, A. Plant Foods and Herbal Sources of Resveratrol. *J. Agric. Food Chem.* 2002, 50, 3337–3340. [CrossRef] [PubMed]

84. Dubin, K.; Callahan, M.K.; Ren, B.; Khanin, R.; Viale, A.; Ling, L.; No, D.; Gobourne, A.; Littmann, E.; Huttenhower, C.; et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. *Nat. Commun.* 2016, 7, 10391. [CrossRef] [PubMed]

85. Chaput, N.; Lepage, P.; Coutzac, C.; Soulard, E.; Le Roux, K.; Monot, C.; Boselli, L.; Routier, E.; Cassard, L.; Collins, M.; et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann. Oncol.* 2017, 28, 1368–1379. [CrossRef] [PubMed]

86. Chen, L.; Jiang, B.; Zhong, C.; Guo, J.; Zhang, L.; Mu, T.; Zhang, Q.; Bi, X. Chemoprevention of colorectal cancer by black raspberry anthocyanins involved the modulation of gut microbiota and SFRP2 demethylation. *Carcinogenesis* 2018, 39, 471–481. [CrossRef] [PubMed]

87. Gopalakrishnan, V.; Spencer, C.N.; Nezi, L.; Reuben, A.; Andrews, M.C.; Karpinets, T.V.; Prieto, P.A.; Vicente, D.; Ullah, M.F.; Khan, M.W. Food as medicine: Potential therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac. J. Cancer Prev.* 2008, 9, 187–195. [PubMed]

88. Matson, V.; Fessler, J.; Bao, R.; Chongsuwat, T.; Zha, Y.; Alegre, M.L.; Luke, J.J.; Gajewski, T.F. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018, 359, 97–103. [CrossRef]

89. Ullah, M.F.; Khan, M.W.; et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Future Oncol.* 2020, 16, 359, 1287. [CrossRef] [PubMed]

90. Ullah, M.F.; Khan, M.W. Food as medicine: Potential therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac. J. Cancer Prev.* 2008, 9, 187–195. [PubMed]

91. Matson, V.; Fessler, J.; Bao, R.; Chongsuwat, T.; Zha, Y.; Alegre, M.L.; Luke, J.J.; Gajewski, T.F. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018, 359, 97–103. [CrossRef]

92. Catalákyaya, G.; Venera, K.; Lucini, L.; Rocchetti, G.; Delmas, D.; Daglia, M.; De Filippis, A.; Xiao, H.; Quiles, J.L.; Xiao, J.; et al. Interaction of dietary polyphenols and gut microbiota: Microbial metabolism of polyphenols, influence on the gut microbiota, and implications on host health. *Food Front.* 2020, 1, 109–133. [CrossRef]

93. Anhê, F.E.; Pilon, G.; Roy, D.; Desjardins, Y.; Levy, E.; Marette, A. Triggering Akkermansia with dietary polyphenols: A new weapon to combat the metabolic syndrome? *Gut Microbes* 2016, 7, 146–153. [CrossRef] [PubMed]
