The Potency of Herbal Active Compounds as Immune Modulators for Cancer Therapy

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ABSTRACT
Cancer was the second leading cause of death globally in 2018. On the other hand, immunotherapy is one of the most promising and effective therapies to fight against cancer. This area of research has highly increased over the last decade. Immunotherapy will modulate and initiate an effective immune response. Hence, the immune system in the body will be more potent in combating cancer. Cancer immunotherapy can utilize herbal products to modulate the immune system with low toxicity. In addition, the usage of herbal products has also proven to decrease the side effects of conventional cancer therapy. Some herbal products have been proven to have biological and pharmacological activity, such as anti-inflammatory, anticancer, and chemopreventive. Indonesia, with its immense biodiversity of herbal products, can use this advantage to develop these sources in the health sector. We showcase some active compounds such as quercetin, andrographolide, curcumin, resveratrol, capsaicin, epigallocatechin-3-gallate, genistein, 6-shogaol, and 6-gingerol. We further highlight the mechanism and signaling pathways that can occur in these active compounds to suppress cancer progression and development. This review discusses the mechanism and potency of herbal products as a modulator in cancer immunotherapy to combat cancer. In summary, this review summarizes herbal products’ active compounds and future promise within the field of immunotherapy.

INTRODUCTION
In 2018, around 9.6 million people died from cancer, and 300,000 new cancer cases were diagnosed each year among children at age 0-19 years [1]. Along with the development of technology and knowledge in health and medicine sectors, the hallmarks of cancer was updated this year and consists of 14 characteristics including cancer characteristic with avoiding immune destruction [2]. Immune escape is one of the essential factors in tumorigenesis including tumor cells that are resistant to immune response, abnormalities in immune cells such as T cells, and immunosuppressive tumor microenvironment. Many mechanisms available within immune escape will enhance the capability of current cancer therapy, mainly to improve cancer immunotherapy that achieves massive success from a subset of cancer patients [3].

Cancer immunotherapy works on distinct types of cancer and offers the possibility of long-term cancer remission [4]. This is because the immune system can be activated, target cancer cells, and the immune system can be trained to remember cancer cells. Cancer immunotherapy also concentrates on the immune system and works more specifically than conventional treatment. The side effects of immunotherapy itself also vary and depend on which type of immunotherapy is used. Meanwhile, conventional cancer treatments have many adverse effects on chemical or radiological therapy on cancer issues [5].

Indonesia is famous for being a country with a great abundance of natural resources and mega biodiversity [6]. This potency makes Indonesia able to develop various medicine that comes from its natural resources. Natural products can also show great potential in cancer immunotherapy. Natural products can be obtained from nature with compounds extracted and optimized from natural resources. There are some natural products such as curcumin and saponin combined with cancer immunotherapy that Food and Drug Administration (FDA) has approved to continue with clinical trials [7]. Natural products also show some beneficial activities in suppressing the progression and development of cancer cells. Many natural compounds have biological activities such as anti-inflammatory, anticancer, and proapoptotic [8].

Besides, natural products are also considered immune-modulating agents. Immune modulating agents can increase immune response and are considered as one of the immunotherapy against cancer. Herbal
Herbal Compounds as Immune Modulators in Cancer Therapy

MARIA MAGDALENA & SEPTELIA INAWATI WANANDI

Herbal active compounds can also modulate the immune response and contribute to pharmacotherapy [9]. On the other hand, the occurrence of resistance to treating cancer by using chemotherapy is increasing [10]. By using DNA alkylating agents, antimetabolites, and inhibitors, tumors may be resistant to some types of cytotoxic drugs. This mechanism may occur because of the modified transport of the drug across the plasma membrane, improved DNA repair, genetic responses, an adjustment in target molecules, access to target cells, metabolic effects, and growth factors [11]. Herbal products are also low in toxicity, have low side effects, and can be considered as the new active compound to avert the occurrence of resistance by using the conventional method to cure cancer [12]. These advantages make natural products a good candidate for immunotherapy.

This review aims to discuss herbal products that can be used as modulators for cancer therapy and their mechanism in modulating the immune response. A better understanding of the proposed mechanism in some natural compounds is also essential to develop the future of herbal products. First, this review will discuss current cancer immunotherapy. Next, herbal active compounds will be discussed further and mainly emphasize the advantages to be used as an immunomodulator for cancer therapy. Then, the potential herbal products as immunomodulators are summarized and explained with the difficulties also overcoming problems that can be faced by developing natural products such as cancer immunotherapy. Finally, the future perspective of cancer immunotherapy using herbal active compounds is discussed in the last part.

Cancer immunotherapy

Nowadays, new approaches used to cure cancer have been invented. One of them that shows a promising result is immunotherapy. Before immunotherapy was invented, patients with cancer underwent standard care such as surgery, radiotherapy, and chemotherapy [13]. Immuno-oncology has been transforming into one of the standards of care to cure cancer. The most crucial role in cancer immunotherapy is T cells [14]. T cell-based immunotherapy can be very promising by targeting the tumor microenvironment (TME) [15]. Besides that, IDO (Indolamine 2,3-dioxygenase) inhibitors, the usage of an oncolytic virus, Car-T cells, and cancer vaccines make cancer immunotherapy promising to cure cancer [16].

Indolamine 2,3-dioxygenase (IDO) has been viewed as a crucial mechanism for cancer immune escape [17]. Hence, IDO inhibitors will be a promising therapeutic potential. The development of IDO-mediated immunosuppressive effects will be a promising approach to elevate the level of immunosuppressive regulatory T cells. The suppression of IDO1 activity is an interesting target for cancer treatment to recover tumor immunity. Oncolytic viruses can be used for cancer immunotherapy since the viruses can infect and destroy cancer cells. Tumors that the immune system cannot recognize can be made immunogenic by oncolytic viruses [18].

Nowadays, Car T cells also enhance the ability of a patient’s immune system to destroy cancer cells. Car T cell therapy uses T cells because they play an essential role in controlling the immune response and killing pathogen-infected cells [19]. T cells will be genetically engineered to produce receptors called chimeric antigen receptors (CARs). This receptor will make T cells recognize and attack to antigens such as cancer cells [20]. Meanwhile, cancer vaccines have an objective response rate below 5% in most trials [21]. Current cancer vaccines may be improved when combined with checkpoint inhibitors or novel immunostimulatory agents. For example, dendritic cell vaccination will improve the activation of tumor-specific T cells and kill tumor cells [22]. However, the challenges are resistance and immune suppression. There are several checkpoint antibodies in cancer immunotherapy such as Anti-PD-L1, Anti-PD-1, and Anti-CTLA-4 [23].

So many challenges that may be faced by cancer immunotherapy. These challenges include unpredictable efficacy, so there are significant variabilities in patient response. An active compound that is consistently sufficient to cure many cancer types and patients’ conditions should be developed. Additional biomarkers and various tumor antigens are also essential to be identified. Hence, the tumor can be easily detected by the immune system and the immune system response will be triggered. Tumor heterogeneity also will be a major challenge since this issue will have clinical implications such as sampling issues and therapeutic response [24]. The other challenge is that resistance to drug treatment will arise. The financial issue will also be a problem since drugs for immunotherapy are expensive.

On the other hand, immunotherapy can be combined with conventional cancer therapy and targeted therapy. For example, a combination of conventional cancer treatment such as chemotherapy. Chemotherapy, along with various types of cancer treatment, can be used independently or with other treatments [25]. Some research findings have already shown that using a combination of chemotherapy and immunotherapy as a first strike toward Non-small cell lung cancer (NSCLC) can be a great solution. It will help the immune system to find and kill cancer cells [26]. Besides that, cancer immunotherapy will be combined with radiation and can start an immune response to kill cancer cells [27].

Unlike chemotherapy, cancer immunotherapy treats patients with their immune systems. Immunotherapy modulates their immune response and boosts the immune response. It makes the immune system know how to identify, target, and destroy cancer cells. Meanwhile, chemotherapy uses drugs to kill cancer cells and attack all cells that proliferate within the body.
This will attack both cancerous and non-cancerous cells. Hence, the side effects of chemotherapy are more significant than immunotherapy. Regarding efficacy, cancer immunotherapy also can make a memory for immune cells and can be maintained even after the treatment has been already finished [28].

On the other side, chemopreventive agents are substances that have anticancer characteristics to prevent carcinogenesis by blocking DNA damage in the initiation stage or reversing the processes at stages of promotion and progression. The effectiveness of this cancer chemoprevention can be included in natural products that exist in food. Based on the inhibition stage, chemopreventive agents can be separated into two categories such as blocking agents and suppressing agents [29]. Blocking agents will prevent any carcinogenic substance such as interaction or activation with DNA, RNA, or protein in the initiation stage and destroy the carcinogen from reaching the target sites. Suppressing agents will inhibit the cells that are being initiated to develop into malignant cells at the promotion or the progression stage [30].

**Herbal active compounds**

Herbal products can be divided into two major classes that consist of primary and secondary metabolites [31]. Primary metabolites are organic molecules that are needed for an organism’s survival to produce this metabolite. In the meantime, the secondary metabolites are organic compounds with an external function that influences some other organisms [32]. Terpenoids, phenolic compounds, and alkaloids are the major categories in secondary metabolites [33]. These compounds especially terpenoid and phenolic compounds like flavonoids, play a crucial role in biological and pharmacological properties [34]. Therefore, developing effective and selective methods for the extraction and isolation of these bioactive herbal products is crucial. For example, several methods have been used such as reflux extraction as the most common method. Supercritical fluid extraction (SFC), pressurized liquid extraction (PLE), and microwave-assisted extraction (MAE) have been applied in herbal product extraction [35].

Some herbal products can have interesting biological and pharmacological activity such as resveratrol, curcumin, capsaicin, andrographolide, quercetin, and genistein. Many natural compounds have biological activity such as anti-inflammatory, anticancer, and proapoptotic to cure cancer [36]. Herbal active compounds can be a substitute for chemotherapy and have proven to decrease the side effects of conventional chemotherapy. Taxol or known as Paclitaxel was acknowledged as a natural-source cancer drug and extracted from the Pacific Yew tree (Taxus brevifolia).

So far, these active herbal compounds have been used to treat breast, lung, and ovarian cancer [37].

Natural products such as herb extracts also have been reported to effectively reduce the side effects caused by chemotherapy [38]. Cortex *Phellodendron chinensis* (CPC) as well as Cortex *Phellodendron amurense* (CPA) from the dried bark of *Phellodendron chinense* Schneid. or *P. amurense* Rupr., have been known to reduce neurotoxicity side effects from chemotherapy [39]. Besides, Japanese herbal medicines, called Kampo, have also been reported to have beneficial effects on cancer chemotheraphy-induced side effects [40].

Since nowadays many cancer therapies may cause resistance in some of the drugs. More active and natural compounds that have low toxicity but are effective to inhibit and cure cancer cells are needed. Hence, many developments in cancer drugs are made from herbal products [41]. A better understanding of the proposed mechanism in some natural compounds is also crucial for developing future herbal products. However, Developing these herbal products that can be administered to the human body so they can be effective is also a big challenge for us.

**Potential herbal products as immunomodulators**

Herbal products have characteristics to modulate the immune system. Hence, they can be used as cancer immunotherapy. Since they can modulate the immune system, herbal products can have a suppressed effect (immunosuppressant) and increase the immune system (immunostimulant) [42]. They can also modulate the immune system via multiple components in immune systems. Some of the natural products that have been discussed in this article are shown in Table 1. Besides that, it also has been proven to interfere in many signal transduction cascades and interfere with key regulatory effectors. Many secondary metabolites in plants such as phenolics, alkaloids, saponins, and terpenes, have a direct ability to attenuate macrophage proinflammatory activity [43], activate tumor antigen presentation, and enhance adaptive and innate immune systems [44]. Herbal products also play a role in cell cycle modulators and regulate invasion and metastasis depending on the dose given and the phytochemicals that are being used as the modulator [45].

**Curcumin**

Curcumin is originally from a plant called *Curcuma longa*, which belongs to the ginger family Zingiberaceae. Some of the immunomodulatory effects of curcumin have been found in Figure 1.

As shown in Figure 2, curcumin can target regulatory T cells [70]. Curcumin will be suppressed Tregs activity by inhibiting TGF-β and IL-10 in lung cancer [46]. Curcumin medication will inhibit PD-L1 and p-STAT3 expression in ovarian cancer cells in vitro. In this study,
Table 1. *In vitro* and *in vivo* information on immunomodulatory effects from some natural products

<table>
<thead>
<tr>
<th>Natural Products</th>
<th>Experimental Model</th>
<th>Type of Cancer</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Human Non-Small Cell Lung Cancer treated with curcumin</td>
<td>Non-Small Cell Lung Cancer</td>
<td>↓ Treg, TGF-β, IL-10, ↑ Th1, IFN-γ</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Mice induced with ovarian cancer cell line treated with curcumin</td>
<td>ovarian cancer</td>
<td>↓ PD-L1, p-STAT3, Treg ↑ CD8+ T cells</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>BALB/c mice induced with LPS with 4T1 cells treated with curcumin</td>
<td>breast cancer</td>
<td>↑ CD4+, CD25+, Foxp3+, and Treg</td>
<td>[48]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>JIMT-1 cells treated with resveratrol</td>
<td>breast cancer</td>
<td>↓ PD-1/PD-L1</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>EG7 tumor-bearing C57BL/6 mice treated with resveratrol</td>
<td>lymphoma</td>
<td>↑ IFN-γ, CD8+, CD4+ T cells</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>A549 cells treated with resveratrol</td>
<td>lung cancer</td>
<td>↓ Treg</td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>U87, AGS, MKN45, HS746T cell lines treated with capsaicin in dose and time exposure dependent manner</td>
<td>human glioma and gastric cancer</td>
<td>↓ NKC, IFN-γ, and TNF-α</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>HT29 and RKO cell lines were treated with capsaicin in a dose-dependent manner</td>
<td>colon carcinoma</td>
<td>↑ TNF-α IL-1β, and IL-6</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td>BC3 and BCBL1 cell lines were treated with capsaicin in a dose-dependent manner</td>
<td>lymphoma</td>
<td>↑ DC maturation</td>
<td>[54]</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Murine xenograft model of CT26 treated with andrographolide</td>
<td>colon cancer</td>
<td>↓ PD-1, TNF-α, IL-12, NO, and COX-2</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td>LNCAp, DU145, and PC-3 cells treated with andrographolide</td>
<td>prostate cancer</td>
<td>↓ IL-6</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>LNCAp, C4-2b, and PC-3 cells treated with andrographolide</td>
<td>prostate cancer</td>
<td>↓ CXCL11, CXC3, and CXC7</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>NSCLC cells treated with andrographolide</td>
<td>lung cancer</td>
<td>↑ NKC and inflammatory cytokines</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>RAW264.7 macrophages stimulated with LPS treated with andrographolide</td>
<td>Abelson murine leukemia virus-induced tumor</td>
<td>↓ inflammatory cytokines</td>
<td>[59]</td>
</tr>
<tr>
<td>Epigallocatechin-3-gallate (EGCG)</td>
<td>4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone treated A/I mice</td>
<td>Non-Small Cell Lung Cancer</td>
<td>↓ PD-L1</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>TC-1, B16, and B16E7 cells</td>
<td>melanoma</td>
<td>↑ IFN-γ</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>1205Lu, HS294T and A375</td>
<td>melanoma</td>
<td>↑ CD8+ T cells</td>
<td>[62]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>A549 cells treated with quercetin</td>
<td>lung cancer</td>
<td>↑ TNF-α and IL-8</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>NK-92 and NCIH460 cell line</td>
<td>lung cancer</td>
<td>↑ NKC and inflammatory cytokines</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>MCF-10A, MCF-10AT, MCF-7, and MDA-MB-231</td>
<td>breast cancer</td>
<td>↓ PD-L1, IFN-γ ↑ T cells</td>
<td>[65]</td>
</tr>
<tr>
<td>Genistein</td>
<td>C57BL/6 mice treated with genistein</td>
<td>cervical cancer</td>
<td>↑ IFN-γ, lymphocyte</td>
<td>[66]</td>
</tr>
<tr>
<td>6-shogaol and 6-gingerol</td>
<td>Ethionine-Induced Hepatoma Rats</td>
<td>liver cancer</td>
<td>↓ NFkB and TNF-α</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>Ethionine-Induced Hepatoma Rats treated with ginger extract</td>
<td>breast cancer/liver cancer cells</td>
<td>↓ TNF-α</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>Murine RAW 264.7 macrophages</td>
<td>Abelson murine leukemia virus-induced tumor</td>
<td>↓ COX-2 and iNOS</td>
<td>[69]</td>
</tr>
</tbody>
</table>

Note: Time 1, Treg, regulatory T cell; TGF-β, Transforming Growth Factor-β; IL-10, Interleukin-10; Th1, T helper 1; IFN-γ, Interferon-γ; PD-L1, Programmed Death – Ligand 1; PD-1, Programmed Death – 1; COX-2, Cyclooxygenase-2; NKC, Natural Killer Cell; Foxp3+, Forkhead box P3 +; TNF-α, Tumor Necrosis Factor-α; NO, Nitric Oxide; iNOS, inducible Nitric Oxide Synthase; CXC3, C-X-C Motif Chemokine Receptor 3; CXC11, C-X-C Motif Chemokine Ligand 11; NFkB, Nuclear Factor Kappa B
after analysis with curcumin, CD8+ T cells were elevated and Treg cells were reduced, resulting in an antitumor immune response increase [47]. Another experiment shows that curcumin can reduce inflammatory damage in tumor-bearing hosts as well as increase immune system response through CD4+, CD25+, Foxp3+, and Treg cells [48]. In addition, curcumin will suppress the NF-kB pathway and inhibit Protein Kinase C [71]. This NF-kB pathway has been shown with another experience to inhibit PD-L1 expression. After two weeks of curcumin treatment, Treg cells were decreased and Th1 cells were increased significantly in lung cancer patients. This study concluded that curcumin would increase the alteration of Treg cells to Th1 cells by increasing the expression of IFN-γ and reducing the expression of Foxp3. Th1 cells may activate T cells and facilitate their growth, immune activation, and intracellular microbes [46].

The limitation of curcumin is that this active compound has low solubility in water and low bioavailability [72]. Low bioavailability will affect its potential to fight against cancer. This low bioavailability may have been resolved with low solubility, making it nanoparticles in surfactants such as tween 80. Nanocurcumin aqueous dispersion has proven to be more soluble in water since the curcumin nanoparticle surface area is larger than curcumin. This study was conducted to treat cancer by Yallapu et al in 2012.

Surfactants such as tween 80 were used to stabilize low-solubility molecules and prevent particle aggregation. A low dose of curcumin (50 mg/kg) has been used in tumor cells and proved to inhibit tumor growth by promoting the cytotoxicity of CD8+ T cells. Hence, the curcumin dose should be considered carefully.

**Resveratrol**

Resveratrol is an active compound that we usually find in red wines, grapefruits, and peanuts. Resveratrol also has biological and pharmacological activities such as anticancer, anti-inflammatory, and proapoptotic [73]. These characteristics are useful for treating cancer and have immunomodulatory effects [74]. Resveratrol plays an essential role in immune tumor evasion. Its effect can be seen in **Figure 3**. It can also enhance cytotoxic T cells by inhibiting the PD-1/PD-L1 signaling pathways. Currently, research conducted by Verdura S in 2020 showed that resveratrol could target PD-L1 glycosylation and dimerization to enhance antitumor T-cell immunity [49]. Additionally, resveratrol also can regulate the Tregs population as well as increase IFN-γ expression in CD8+ T cells either in *ex vivo* or *in vivo*. The immune-enhancing activity was found by restoring the CD4+ T cell recognition of B-cell lymphomas and proved that resveratrol can be used to restore the immune defense to prevent cancer recurrence [50,75].
apoptotic activity is mediated via TRPV1 (Transient Receptor Potential Vanilloid 1), a receptor of capsaicin that leads to mitochondrial damage and cytochrome c release. TRPV1 is a positive charge channel in the nociceptive neurons of high Ca2+ preference. This channel will be activated via physical and chemical stimuli such as heat, low pH, and capsaicin. Increased TRPV1 expression will upregulate the inflammatory cytokines such as IL-8 (Interleukin-8), MCP-1 (Monocyte chemoattractant protein-1), and MIP-1α (Macrophage inflammatory protein) α in normal cells [83].

Besides TRPV1, capsaicin also plays a crucial role in the inhibition of the NF-kB pathways. Capsaicin will inhibit proliferation and induce cell-cycle arrest throughout human KB cancerous cells [84]. In human esophageal carcinoma cells, capsaicin induces G0/G1 phase arrest throughout human esophageal carcinomas [85]. Capsaicin also shows that the maturation of DC has been increased in lymphoma cell lines in a dose-dependent manner [54]. Other than the association of TRPV1 activation with proinflammatory responses, the deactivation of the TRPV1 channel from capsaicin also has an anti-inflammatory role in a dose-dependent and exposure-time-dependent manner. It shows that with longer time of exposure (24h) reduces NKC (natural killer cell) performance and cytokine production (IFN-γ and TNF-α) in human glioma cell lines and gastric cancer [52]. TRPV1 might have a protective role by exhibiting higher neutrophils infiltration, and higher serum of TNF-α, IL-1β, and IL-6 cytokine levels when TRPV1 is blocked [53]. This was proven in 2017 by Bessler, et al in carcinoma cell lines. The immunomodulatory effect of capsaicin showed in Figure 4.

Besides, resveratrol suppresses the activation of cancer by inhibiting the NF-kB pathways [76]. Hence, this will inhibit cancer cells to undergo migration, invasion, development of cancer cells, and chemoresistance of cancer cells. Resveratrol also has anti-inflammatory action by inhibiting COX-2 [51]. This will decrease proinflammatory factors and increase anti-inflammatory factors such as IL-10 [77]. VEGF expressions also will be lessened by resveratrol. This will be impacted to reduce its ability of angiogenesis [78]. In conclusion, resveratrol can affect tumor-infiltrating immune cells such as cytotoxic T- cells, dendritic cells, Tregs, TAMs (Tumor-Associated Macrophages), and NK cells by either activating or suppressing immune cells in the tumor microenvironment [79]. Resveratrol enhances the susceptibility of cancer cells to immune cells by regulating various cellular signaling events including immune cell regulation by modulating cytokine secretion, immune checkpoints, and NF-kB signaling.

Resveratrol itself has several limitations such as low bioavailability of resveratrol, so it will be metabolically eliminated from the body extremely fast. Therefore, it will be challenging to maintain resveratrol at therapeutic levels in the bloodstream and this will decrease the therapeutic efficacy [80]. Still, resveratrol is a promising compound that can be used for the immunomodulatory response. In addition, resveratrol can also be used as an adjuvant and also chemotherapy sensitization agent since resveratrol can enhance radiosensitivity, so there will be a significant increase in cancer treatment by apoptosis and cell autophagy [81].

Capsaicin
Capsaicin can enhance the occurrence of apoptosis. Since apoptosis is a crucial step for cure cancer, Bley et al in 2012 reviewed that 40 different cancer lines have been induced apoptosis by capsaicin [82]. This apoptotic activity is mediated via TRPV1 (Transient Receptor Potential Vanilloid 1), a receptor of capsaicin that leads to mitochondrial damage and cytochrome c release. TRPV1 is a positive charge channel in the nociceptive neurons of high Ca2+ preference. This channel will be activated via physical and chemical stimuli such as heat, low pH, and capsaicin. Increased TRPV1 expression will upregulate the inflammatory cytokines such as IL-8 (Interleukin-8), MCP-1 (Monocyte chemoattractant protein-1), and MIP-1α (Macrophage inflammatory protein) α in normal cells [83].

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Many researchers conclude that the TRPV1 activator resulted in a synergistic effect with suppression of tumor cell migration and was associated with a significantly higher level of apoptosis in human breast cancer cells.
Andrographolide is an active compound from Andrographis paniculata. Andrographolide is proven to have an immunomodulatory effect on cancer (Figure 5). It has been used as traditional medicine, especially its leaves and roots. An abundant amount of andrographolide has been found in its leaves. Meanwhile, there are more flavonoid compounds in the roots than andrographolide [87].

Immunomodulatory activities were found in this compound, including the reduction of TNF-α (Tumor necrosis factor), IL-12, NO (Nitric oxide), and COX-2 (Cyclooxygenase). TNF-α plays a significant role in curing cancer as an anticancer factor and as an immunosuppressive cytokine [88]. TNF can induce activation-induced cell death (AICD) of CD8+ T cells. Andrographolide was also found to inhibit tumor growth in prostate cancer by modulating proinflammatory cytokines (IL-6) [56] and chemokines (CXCL11, CXCR3, and CXCR7) [57]. NF-κB pathway will also be inhibited by andrographolide to decrease the proinflammatory protein expression. Andrographolide will enhance NK cell activity and maturation of dendritic cells to induce antigen-specific tolerance [58,89]. In the innate immune response, macrophages will be activated. Macrophages in the microenvironment will take a crucial role in producing proinflammatory cytokines. This reaction is also essential to the development of cancer. Classical and alternative activation of macrophages will be modulated by andrographolide [55]. Andrographolide can regulate specific antibody production and show promising results for immunomodulatory drugs.

Macrophage phenotypic polarization and antigen-specific antibody production are regulated. Hence, andrographolide can modulate innate and adaptive immune responses. It can play a role in inhibiting the activated inflammatory signaling pathways [59]. Some challenges may be faced by andrographolide. Andrographolide also has low bioavailability because it can undergo rapid biotransformation. A structural modification was the way to enhance the bioavailability of andrographolide [90]. Using halogen as substituents on the andrographolide structure will improve its potency to fight cancer cells or the removal of OH in andrographolide unfortunately will increase the activity [91].
Epigallocatechin-3-gallate (EGCG) is a major polyphenol that can be found in green tea (Camellia sinensis) (Figure 6). Green tea will be beneficial for anti-inflammatory which is consumed for its immunomodulatory effects [92]. Green tea extract that contains EGCG will inhibit PD-L1 expression. In the adaptive immune response, research conducted in vivo shows that cytokines secretion such as IFN (Interferon)-γ increased significantly [60,93]. In fighting cancer cells, EGCG has been reported because its anti-angiogenic, anti-invasive, anti-proliferative, and chemopreventive in vivo and in vitro [94]. EGCG will limit the activation of the NF-kB.

Previously, it has been reported that EGCG can elevate the amount of CD8+ T cells in an in vivo tumor model and increase the number of CD8+ CTLs infiltrating the TME [95]. EGCG also induces direct cytotoxicity on tumor cells and enhances the production of IL-12 to induce Th1 response against tumors [96]. In research on lung cancer growth, EGCG can suppress the PD-L1/PD-1 signaling pathways, hence restoring the killing ability of T cells [62]. In 2021, Schwager et al reported that EGCG led to an increased proportion of CD8+ lymphocytes and favored secretion of Th1 cytokines [61]. This research concludes that EGCG modulates activated T lymphocytes which help to combat cancer cells.

Figure 6. EGCG molecular structure and Camellia sinensis plant as sources for EGCG

The limitation of EGCG is its poor bioavailability because of the instability of EGCG in alkali and neutral conditions, low cellular uptake, metabolic transformation, and active efflux of many polyphenolic compounds [97]. EGCG bioavailability will be improved using a pro-drug approach. The development of EGCG has been used for different packaging such as nanophytosome. The implementation for this nanophytome usage in capsaicin application is in drug delivery.

Quercetin

Quercetin was found in a variety of food such as broccoli, berries, apples, tea, and grapevines (Figure 7). Herbal compounds like quercetin have been regarded as critical preventative and recovery agents for cancer due to their efficacy, high therapeutic, and low toxic effects. It will target proinflammatory signaling pathways such as MAPK (mitogen-activated protein kinase) and NF-kB [98]. Quercetin can modulate the immune system to eliminate cancer cells (Figure 8).

Research in 2016 shows that quercetin has a long-lasting anti-inflammatory substance and immunosuppressive effect on dendritic cell functions. Unfortunately, a study in vitro using lung A549 cell lines shows that it can induce TNF-α production in macrophages and IL-8 production [63]. Quercetin also can increase the production of Th-1 derived interferon-γ.

Figure 7. Quercetin sources in a variety of food
Genistein

Genistein is a bioactive compound found in soy and soy-derived items. Genistein is an isoflavone, a class of flavonoids abundantly found in soy products [102]. The structure of the genistein and soybean plant can be seen in Figure 9.

Genistein will strongly inhibit angiogenesis and inhibit the proliferation of cancer cells. Genistein will also induce apoptosis. It has been proven before by Ghaemi et al that genistein can induce a protective immunomodulatory effect in a mouse model of cervical cancer by increasing IFN-γ [66]. Genistein inhibits the activation of NF-kB and Akt signaling pathways since NF-kB continues to play an important role in the regulation of cell division, differentiation, apoptosis, and stress response [103]. Genistein could modulate NF-kB DNA binding interaction in breast, pancreatic, prostate, head, and neck cancer cells as well.

Research has found that genistein can enhance the antitumor activity of chemotherapy agents via NF-kB regulation. Some established chemotherapy agents may stimulate NF-kB activation, such as cisplatin as well as gemcitabine. These agents may also be accountable for drug resistance in cancerous cells. After the cells are pre-treated with genistein, research in vivo and in vitro found that NF-kB will be inactivated and together with and regulates Th-2 derived by IL-4 [99]. This study concludes that quercetin has immune-stimulatory effects. It can block IL-6 secretion, affects immunity and inflammation by targeting many signaling pathways, and work on leukocytes. In another study from in vitro treatment, quercetin activated T cells, NK cells, and blocked IL-12 [64]. Hence, this research will show T cell proliferation and Th1 differentiation.

In breast cancer cell lines, quercetin has decreased PD-L1 protein and increased IFN-γ protein [65]. Currently, quercetin is investigated to cure prostate cancer and focuses its research on increasing animal survival. Numerous studies have repressed the proliferation of gastric, breast, colorectal, oral, liver, thyroid, pancreatic, lung cancer, and leukemia [100].

Some challenges may be faced in developing quercetin as cancer immunotherapy. Although many advantages are mentioned, quercetin has also been constrained due to its low solubility in water and lack of stability in physiological conditions with low bioavailability. Quercetin analogs have been shown to have better solubility. Hydroxyl groups of this herbal compound may be substituted by various combinations such as esters, ethyl, and benzyl ethers [101]. These analogs can be examined along with docking analyses to know their advantages and safety of these analogs.

Figure 8. Immunomodulatory effects of quercetin

Figure 9. Molecular structure of genistein and soybean plant
non-toxic doses of chemotherapeutic agents, will increase the inhibition of cell growth [104]. In 2019, genistein was examined for its effect on NK cell signaling and function. This research shows that genistein will decrease IL-12/IL-18-induced IFN-γ production in PBMCs [104]. Another study by Chen, et al in 2018 shows that genistein can inhibit TLR4 activation [105]. This activation will lead to decreasing production of TNF-α and type 1 IFN. Hence will lead to inflammation and ROS production.

The challenge that may be faced by the development of genistein is the limitation of bioavailability after oral administration because of its poor solubility in water. Genistein also has a bitter taste. The formulation for overcoming these challenges may be complicated [106]. Recently, genistein has also been identified as an adjunct therapeutic drug in combinatorial cancer therapy [107].

6-shogaol and 6-gingerol

6-shogaol and 6-gingerol have anti-inflammatory activity and are related to NF-κB. 6-shogaol can show protective effects on TNF-α and suppressed NF-κB pathways [67,108]. A ginger extract containing 6-shogaol and 6-gingerol will increase levels of anti-inflammatory cytokines, including IL-10, and lower proinflammatory cytokines like TNF-α, NO, and IL-6 [109]. In addition, these bioactive compounds have been investigated for various types of cancers including breast, cervical, colorectal, and prostate cancer. Induction of apoptosis in cancer will also occur with these bioactive compounds.

6-shogaol is formed from 6-gingerol by dehydration and acts as one of the main bioactive. 6-shogaol works as an anti-inflammatory compound by inhibiting leukocyte infiltration into inflamed tissue in vivo [68]. It also can reduce inflammatory mediator systems such as COX-2 or iNOS [69]. They also can act as anti-inflammation and chemoprevention by inhibiting TLR4 activation. In vivo and in vitro research showed that serum levels of inflammatory cytokines such as IL-4, IFN-γ, and IL-17 could be decreased [110]. It’s reported that 6-shogaol is more potent than 6-gingerol in inhibiting breast cancer cells.

Future Perspectives

To understand the advancement of cancer immunotherapy and its development, we have managed to analyze a scientometric review of the development in cancer immunotherapy. All associated research articles from 1979 until 2022 from one of the most trusted bibliometric database websites (Scopus) have been collected. A scientometric analysis is an unbiased approach for critically reviewing research trends and contributions in any area of interest. This study will help new researchers in this field and research grant committees find this work helpful in providing an analysis of the progress in this research area from different mindsets and points of view.

Cancer immunotherapy using herbal active compounds was first developed in 1979. Figure 10 clearly describes that interest in developing cancer immunotherapy with herbal active compounds increases exponentially. The annual publication trend increased from 1979 until its peak in the 2020s. Although there were some declines in some years and this phenomenon was understandable because this research requires sophisticated experiments and involves a broad region of major studies. Meanwhile, the citation trend reached its peak in 2012. In 2012, 8 documents had citations of more than 100. This concluded that there are many high-quality articles published in 2012.
Considering this trend, using herbal active compounds as cancer immunotherapy has attracted researchers’ attention to learn more about this topic. Some problems still appear in this field: (i) Due to low bioavailability, many researchers currently have to improve how these natural products target cancer cells, (ii) Natural products that have been discussed in this paper can modulate various cytokines and chemokines. Therefore, future perspectives may include the discovery of new analogs and derivatives of these natural products that can have more immunomodulatory properties and combine with other therapies can provide a more effective strategy and safer approach for patients, (iii) Many of these natural products are also based on the dose-dependent manner and there are many characteristics from each patient, tumor heterogeneity, and TME differences. Hence, it is important to do more research in pre-clinical or clinical trials.

CONCLUSIONS

Cancer immunotherapy was one of the most promising approaches to inhibit cancer development. Knowledge about cancer immunotherapy continues to grow until this year which indicates that cancer immunotherapy has high interest among researchers, especially in Asia. Using herbal products that can be found in daily food such as quercetin, genistein, resveratrol, curcumin, capsaicin, epigallocatechin-3-gallate, 6-gingerol, and 6-shogaol will have many advantages. Besides their low side effects, these herbal products also can modulate the immune system with a variety of different mechanisms. Future development for these herbal products to improve drug delivery and low availability are the challenges. Hence, knowledge and innovation to make these herbal products more effective still need to be considered.

DECLARATIONS

Ethics approval
Not applicable

Competing interest
The authors declare no competing interest in this study

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