Exploration of Drug Science

Open Exploration

Open Access Review

Harnessing the immunomodulatory potential of natural products in precision medicine—a comprehensive review

Maya G. Pillai, Helen Antony*

Department of Biochemistry, University of Kerala, Thiruvananthapuram 695581, Kerala, India

***Correspondence:** Helen Antony, Department of Biochemistry, University of Kerala, Kariavattom Campus, Thiruvananthapuram 695581, Kerala, India. helenabios@keralauniversity.ac.in

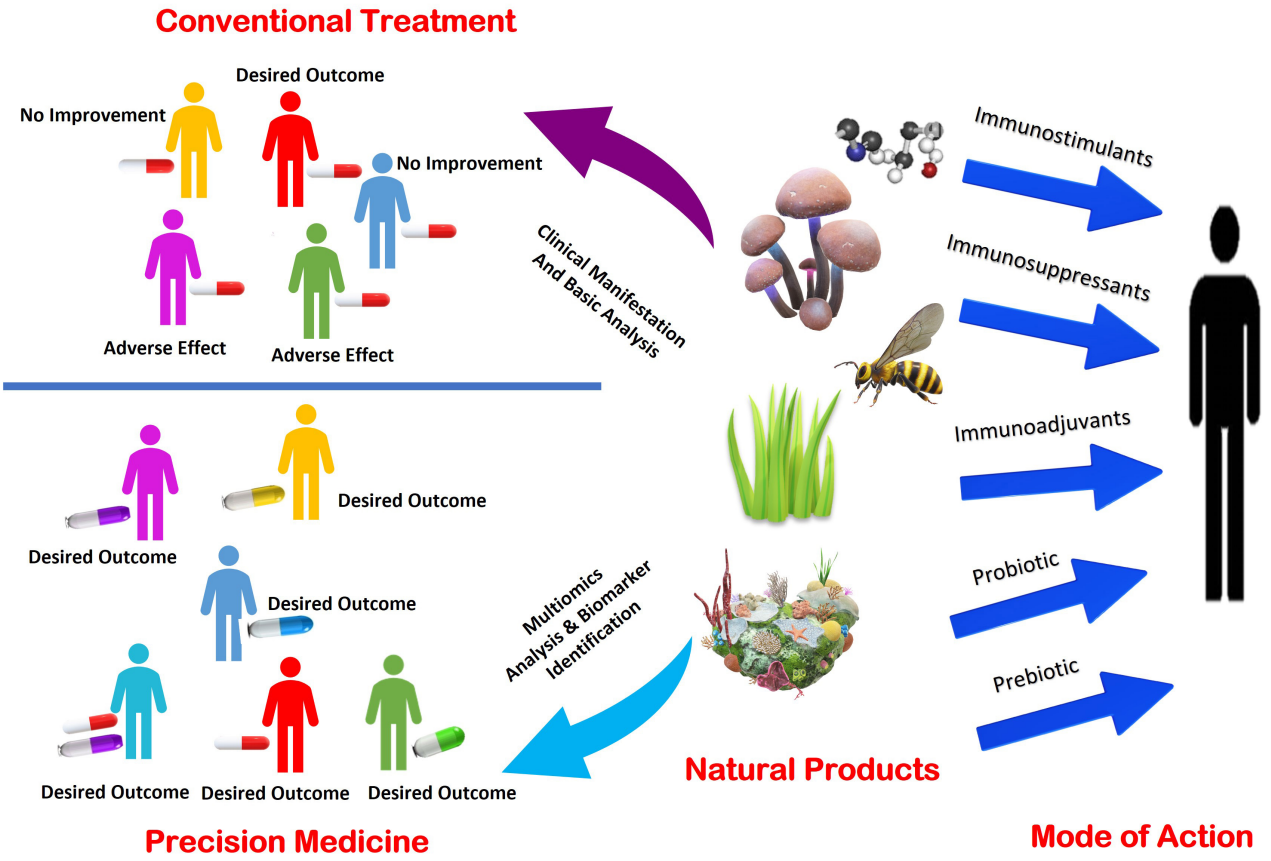
Academic Editor: Juergen Reichardt, James Cook University, Australia

Received: March 4, 2024 **Accepted:** April 25, 2024 **Published:** June 27, 2024

Cite this article: Pillai MG, Antony H. Harnessing the immunomodulatory potential of natural products in precision medicine—a comprehensive review. Explor Drug Sci. 2024;2:339–60. https://doi.org/10.37349/eds.2024.00050

Abstract

Traditional medicine systems worldwide utilize natural products (NPs), including plant-derived compounds, minerals, and organisms, harnessing their healing potential. NPs offer a rich source of potential drug candidates, driving innovation in drug discovery. Recent breakthroughs have reignited interest in harnessing the therapeutic benefits of natural compounds. Clinical applications of NP-based immunotherapies, such as curcumin and resveratrol in cancer treatment, highlight their diverse pharmacological properties. However, despite these advancements, challenges persist in the clinical implementation of NPs. Issues such as standardization, regulatory approval, and supply sustainability remain significant hurdles. Overcoming these limitations requires a concerted effort to address the complexities of NP drug development. Nevertheless, ongoing research efforts and interdisciplinary collaboration hold promise for advancing NP-based therapeutics, paving the way for the development of innovative treatments for various diseases. In the world of precision medicine, a new chapter unfolds as NPs join the therapeutic journey. The exploration of NPs as sources of bioactive compounds has revealed promising prospects for precision therapeutics in medicine. This article explores the therapeutic potential of NPs within the context of precision medicine. It examines the intricate pathways through which bioactive compounds derived from nature offer tailored therapeutic prospects, emphasizing their role in precision medicine interventions. Exploring the synergy between NPs and precision therapeutics at a molecular level, this article delineates the exciting prospect of customized treatments, signifying a transformative impact on modern medical care. The review article further highlights their potential in tailoring treatments based on individual genetic makeup and disease characteristics. Additionally, it discusses challenges and prospects, addressing issues of sourcing, standardization, scalability, and regulatory considerations to realize the full therapeutic potential of NPs.



Graphical abstract. Revolutionizing drug development: conventional treatment vs. precision medicine utilizing natural sources

Keywords

Precision medicine, natural products (NPs), bioactive compounds, tailored therapies, immunomodulation

Introduction

Natural products (NPs) have been used in healthcare systems since ancient times, drawing from the rich biodiversity and traditional knowledge of different cultures. NPs, derived from diverse biological sources including plants, fungi, and marine organisms, have long served as reservoirs of bioactive compounds with profound effects on immune function. Historically, drug discovery has been closely linked to NPs. Traditional medicines are effective treatments for various health conditions, such as malaria, pain, and cancer [1]. Today, there is a renewed interest in exploring the bioactive compounds found in nature. Over the past decades, research efforts have revealed many bioactive compounds from natural sources that possess immunomodulatory properties. These compounds exhibit a spectrum of effects, ranging from potent immunostimulation to immunosuppression, thereby offering versatile tools for the treatment of various immune-related disorders. Notably, the advent of advanced analytical techniques has facilitated the identification and characterization of key bioactive constituents, enabling a deeper understanding of their mechanisms of action and therapeutic potential. The applications of modern techniques, such as multi-omics, network pharmacology, and DNA barcoding, help to validate and document the pharmacological and phytochemical aspects of traditional medicine [2].

Many NPs have contributed to the development of modern drugs, such as aspirin, artemisinin, and vincristine. However, the scientific validation and standardization of NPs are still challenging and require interdisciplinary approaches and evidence-based methods. Precision medicine, characterized by tailored therapeutic interventions based on individual genetic, molecular, and clinical profiles, has emerged as a paradigm shift in healthcare delivery. The complex interplay between the immune system and human health has prompted significant interest in harnessing the immunomodulatory properties of NPs for

precision medicine applications. This growing field represents a convergence of traditional knowledge and modern scientific approaches, aimed at elucidating the therapeutic potential of NPs in modulating immune responses with precision and efficacy. By leveraging the diversity and complexity of NP chemistry, clinicians can envision a future where personalized immunotherapy strategies are tailored to the unique immunological landscape of each patient.

This review aims to provide a comprehensive overview of the current state-of-the-art in harnessing the immunomodulatory potential of NPs within the context of precision medicine. Furthermore, we will discuss emerging strategies for integrating NP-based immunotherapies into clinical practice, with a focus on personalized treatment approaches and future directions for research and development. In summary, this review underscores the pivotal role of NPs in shaping the future of precision immunotherapy and tries to unlock new avenues for therapeutic innovation and ultimately enhance the management of immune-related disorders.

Biological diversity of natural sources

NPs are organic compounds derived from living organisms, such as plants, fungi, and marine organisms. They exhibit remarkable structural and functional diversity and have been a rich source of bioactive molecules for drug discovery and development. NPs have played a vital role in the treatment of various diseases, such as cancer, infectious diseases, inflammation, and neurodegenerative disorders.

Plants are a rich and diverse source of NPs, which have been utilized for healing purposes in various traditional medicine systems, such as Ayurveda, Chinese medicine, and Unani medicine for a long time. Plants synthesize a variety of secondary metabolites, such as alkaloids, flavonoids, terpenoids, phenolics, and glycosides, that exhibit different biological activities and therapeutic potentials (Table 1). Some well-known drugs derived from plants include aspirin, morphine, quinine, vincristine, and artemisinin. Plant NPs can influence the immune system by modulating innate and adaptive immunity, cytokine secretion, inflammation, and cell signaling [2–4].

Table 1. Plant-derived natural products (NPs) with immunomodulatory effect

Major source	NP	Mode of action	References
Aloe vera	Acemannan	• Stimulates the production of interleukin-1 alpha (IL-1α), tumor necrosis factor alpha (TNF-α), IL-6, nitric oxide (NO), and prostaglandin E2 (PGE2) by macrophages • Enhances macrophage phagocytosis • Exhibits antiviral activity • Induces tumor cell apoptosis or necrosis	[5–9]
Withania somnifera	Withanolides	• Comprehensive approach to modulating cellular processes • Potential for therapeutic interventions across various diseases • Targeting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway • Targeting signal transducers and activators of transcription (STAT) pathway • Targeting ubiquitin proteasome pathway	[10–12]
Astragalus membranaceus	Astragalosides	• Upregulates mRNA and Bcl-2 protein expression • Downregulates monocyte chemoattractant protein (MCP) and NF-κB protein expression • Suppresses Bax, cleaved caspase-3, IL-1β, IL-6, and TNF-α expression	[13–15]
Berberis vulgaris	Berberine	• Restricts DNA replication • Inhibits the cell cycle progression • Promotes apoptosis	[16–18]

Table 1. Plant-derived natural products (NPs) with immunomodulatory effect (*continued*)

Major source	NP	Mode of action	References
		• Inhibits inflammatory pathways mediated by NF-κB and activator protein-1 (AP-1)	
		• Suppresses the expression of chemokines, preventing leukocyte migration	
Betula pubescens and *Bacopa monnieri*	Betulinic acid	• Modulates key inflammatory modulators including cyclooxygenase-2 (COX-2), intercellular adhesion molecule-1 (ICAM-1), IL-1β, IL-6, IL-12, MCP-1, PGE2, and TNF	[19–22]
		• Inhibits NF-κB and mitogen-activated protein kinase (MAPK) pathways	
		• Stimulates the production of IL-10	
Boswellia serrata	Boswellic acids	• Induces pro-inflammatory cytokines such as TNF-α, IL-1β, IL-2, IL-4, IL-6, and interferon gamma (IFN-γ)	[23–25]
		• Enhances phagocytosis of macrophages	
		• Modifies antibody production	
		• Inhibits the classical complement pathway	
Boswellia sacra	Frankincense	• Regulation of metabolic profiling	[26–28]
		• Modulation of the MAPK signaling pathway	
Curcuma longa	Curcumin	• Inhibits COX-2	[29–31]
		• Suppresses inducible NO synthase (iNOS)	
		• Blocks lipoxygenase (LOX)	
Camellia sinensis	Epigallocatechin gallate	• Epidermal growth factor receptor (EGFR), Janus kinase (JAK)/STAT, MAPK, NF-κB, and PI3K-Akt-mammalian target of rapamycin (mTOR), influencing gene, protein, and enzyme activity in disease regulation	[32, 33]
		• Interacts with molecules like Toll-like receptors (TLRs), NOD-like receptor protein 3 (NLRP3) inflammasomes, and gut microbiota, impacting the immune system and gut-brain axis	
Tanacetum parthenium	Parthenolide	• Inhibits activation of inhibitory kappa B (IκB), consequently blocking the activation and release of NF-κB from the cytoplasmic IκB complex	[34, 35]
		• Directly binds to NF-κB, preventing its interaction with DNA	
Allium sativum	Allicin, S-allylcysteine	• Modulates TNF-α, IL-6, IL-1β, transforming growth factor beta (TGF-β), and alpha-smooth muscle actin (α-SMA)	[36, 37]
		• Prevents inflammation and fibrosis in lung tissue	
		• Inhibits increases in TNF-α, IL-6, and TGF-β	
Zingiber officinale	Gingerol, shogaol	• Inhibiting COX-2 and LOX pathways	[38, 39]
Vitis vinifera	Proanthocyanidins	• Modulating the MAPK, Akt, and NF-κB signaling pathways	[40, 41]
Camellia sinensis	Catechins	• Modulating inflammation-related oxidative stress-related cell signaling pathways	[42, 43]
		• Activation or deactivation of key pathways such as NF-κB, MAPKs, and transcription factor	
Ocimum sanctum	Eugenol, ursolic acid	• Inhibits the expression of COX-2 and iNOS, reducing levels of proinflammatory cytokines such as IL-6, TNF-α, and PGE2, and modulating NF-κB expression	[44–46]
		• Downregulates oncogenes cellular myelocytomatosis (*c-Myc*) and Harvey rat sarcoma viral oncogene (*H-ras*), modifies p53 expression, and induces apoptosis by decreasing the transcription activity of E2 promoter binding factor 1 (E2F1)	
Glycyrrhiza glabra	Glycyrrhizin	• Inhibits inflammatory cell activation and function, modulating NF-κB, MAPK, and JAK/STAT pathways	[47, 48]

Table 1. Plant-derived natural products (NPs) with immunomodulatory effect (*continued*)

Major source	NP	Mode of action	References
		• Blocks TLR4 signaling, halting NF-κB activation and cytokine production, while suppressing COX-2 and iNOS expression	
		• Suppresses NLRP3 inflammasome activation, reducing reactive oxygen species (ROS), inhibiting NLRP3 expression, and preventing caspase-1 and IL-1β cleavage	
Olea europaea	Oleuropein	• Attenuates inflammation caused by TNF-α, NO, and PGE2, nitrotyrosine, iNOS, COX-2, and poly(ADP-ribose) polymerase (PARP)	[49–51]
		• Inhibits p65 translocation by blocking IκB phosphorylation in signaling pathway studies	
Citrus fruits, apples, onions, parsley, sage, tea, red wine, olive oil, grapes, dark cherries, and dark berries such as blueberries, blackberries, and bilberries	Quercetin	• Increases peroxisome proliferator-activated receptor gamma (PPARγ) activity	[52, 53]
		• Antagonizes NF-κB or AP-1 transcriptional activation of inflammatory genes	
		• Blocks TNF-α-mediated induction of inflammatory cascades	
Polygonum cuspidatum and *Vitis vinifera*	Resveratrol	• Activation of sirtuin-1 (Sirt-1) is implicated in mediating these effects	[54, 55]
		• Sirt-1, acting as a deacetylase, plays a crucial role in immune tolerance by inhibiting the TLR4/NF-κB/STAT pathway and reducing the production of inflammatory factors	
Rhodiola rosea	Salidroside, rosavin	• Anti-inflammatory and antioxidant activity	[56–58]
		• Modulation of the MAPK/NF-κB pathway, etc.	
Silybum marianum	Silybin	• Inhibition of the IL-6/STAT3 signaling pathway	[59, 60]
Zanthoxylum alatum and *Ruta graveolens*	Skimmianine	• Inhibits neuroinflammation by targeting the NF-κB activation pathway	[61–63]
		• Reduces the production of pro-inflammatory mediators in lipopolysaccharide activated BV-2 microglia, including TNF-α, IL-6, iNOS, and COX-2	
		• Neuroprotective effects by preventing neurotoxicity caused by microglia-conditioned media, as evidenced by increased expression of neuronal microtubule-associated protein 2 (MAP-2) protein	
Petroselinum crispum, *Melissa officinalis*, *Origanum vulgare*, and *Justicia gendarussa*	Apigenin	• Downregulates inflammatory cytokine expression	[64–66]
		• Suppresses AP-1, MAPK, and NF-κB pathways in keratinocytes	
		• Induces autophagy by decreasing mTOR activity	
		• Inactivates Akt and protein kinase C (PKC) activities	
		• Protects cells from oxidative stress-induced cell death	
Panax ginseng	Ginsenosides	• Modulates the immune system	[67–70]
		• Influences expression and activity of cytokines, chemokines, transcription factors, and signaling molecules	
		• Targets NF-κB, STAT3, nuclear factor erythroid 2-related factor 2 (Nrf2), and PPAR pathways	

Plant-derived NPs encompass a diverse range of bioactive compounds that exert immunomodulatory effects, examples include curcumin, known for its anti-inflammatory and immunostimulatory properties [71], and quercetin found in fruits and vegetables, which has shown efficacy in autoimmune disease management [72]. Additionally, apigenin, present in parsley and chamomile, etc., exhibits anti-inflammatory and immunosuppressive effects [73], while skimmianine, derived from various plant sources, has been studied for its immunomodulatory potential [63].

Other NPs like fungi, insects, marine organisms, etc. stand out as a prolific source of NPs renowned for their diverse therapeutic potentials, encompassing antimicrobial, anticancer, antiviral, and

immunosuppressive properties (Table 2). Within these categories lies a spectrum of bioactive compounds, with well-established drugs such as penicillin, lovastatin, and cyclosporine. Penicillin, derived from *Penicillium* sp., remains one of the most widely used antibiotics worldwide, while lovastatin, sourced from *Aspergillus* sp., boasts cholesterol-lowering capabilities alongside its anticancer effects. Cyclosporine, extracted from *Tolypocladium* sp., serves not only as an immunosuppressive agent but also exhibits antiviral properties. Other examples of antimicrobial fungal NPs include griseofulvin, amphotericin B, echinocandin, and caspofungin [74, 75].

Table 2. Other natural products (NPs) with immunomodulatory effects

Source	Taxonomic species	NP	References
Fungi	*Cordyceps sinensis*	Cordycepin	[76, 77]
Insects	*Apis mellifera*	Propolis	[78, 79]
Various species	*Lactobacillus*, *Bifidobacterium*	*Lactobacillus*, *Bifidobacterium*	[80, 81]
Algae	*Spirulina platensis*	Phycocyanin	[82, 83]
Marine organisms	*Haliotis diversicolor*	Abalone *Haliotis* peptide	[84, 85]
	Sargassum fusiform	Fucoidans	[86, 87]
	Algae, yeast, salmon, trout, krill, shrimp, and crayfish	Astaxanthin	[88, 89]
Cartilage	Shark and bovine cartilage	Chondroitin sulfate	[90, 91]
Fish	Fish oil	Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)	[92, 93]

The antiviral properties and immune-boosting effects of polysaccharides derived from bacteria, fungi, and algae have been reported [94]. The mechanisms of action and potential applications of polysaccharides against various viruses, especially severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 have been reported and suggest that microbial and algal polysaccharides can be used as adjuvants, nutrient supplements, and drug delivery systems to prevent and/or inhibit viral infections [95].

Fucoxanthin, derived from brown seaweeds, emerges as a promising natural anticancer compound, targeting key pathways involved in cancer development and progression, such as cell cycle regulation, apoptosis induction, angiogenesis inhibition, and autophagy modulation [96]. Small molecule-based approaches are highlighted as effective means to intervene in critical signaling pathways dysregulated in hepatocellular carcinoma (HCC), offering the potential to lessen key aspects of HCC behavior including proliferation, migration, invasion, metastasis, and recurrence [97]. The apoptotic activity of plant and fungal extracts on cancer cells, isolation of active compounds, their mechanisms of action, and clinical trial status, standardization, and bioavailability, emphasize the need for further research to fully unlock their therapeutic potential in cancer treatment [98].

The anti-inflammatory properties of Betulinic acid, Apigenin and Skimmianine (BASk), a novel drug formulation comprising betulinic acid (B), apigenin (A), and skimmianine (Sk) have been studied and it reveals the molecular mechanism underlying the therapeutic effects of BASk, particularly its involvement in CD36-mediated activation of the Toll-like receptor 2 (TLR2)-NOD-like receptor protein 3 (NLRP3) signaling pathway [99]. Some of the recent studies on NPs are listed in Table 3.

Immunomodulatory effect of NPs

Immunomodulation is the process of altering the immune system by enhancing or suppressing its activity. Immunomodulation can be achieved by various agents, such as cytokines, antibodies, vaccines, and drugs. However, these agents may have adverse effects, such as toxicity, resistance, and immunosuppression. Many NPs have shown significant immunomodulatory and overall health-benefiting effects to humans, with no or minimal toxicity. These NPs offer promising alternatives for immunomodulation, as they can modulate the immune system and participate in various processes of innate and adaptive immunity [100].

Table 3. Some of the recent studies in natural products (NPs)

Sl No	Scientific title	Year	Source register	Web address	Countries
1	Evaluate and compare effect of Platelet Rich Plasma(PRP) and Nutraceuticals in pain management of Post Herpetic Neuralgia	2024	CTRI	https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MTAxNjA4&Enc=&userName=Evaluate%20and%20compare%20effect%20of%20Platelet%20Rich	India
2	Evaluation of the safety and the efficacy of a novel polyherbal mouthwash containing Emblica officinalis,Cinnamomum cassia,Silicate of magnesia,Nigella sativa and Eucalyptus globulus oil in patients with gingivitis:A randomized controlled trial	2024	CTRI	https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=OTM1NDg=&Enc=&userName=CTRI/2024/01/061413	India
3	Beneficial Effects of Specific Natural Products on Management of Xerostomia: A Randomized Controlled Clinical Trial	2024	ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT06217614	Egypt
4	Effect of taking foods containing natural products on mental and physical health in adult women	2023	JPRN	https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000055834	Japan
5	The impact of dietary fibre supplementation on gum disease; A randomised control trial in healthy volunteers	2023	ANZCTR	https://anzctr.org.au/ACTRN12623001067662.aspx	Australia
6	Safety, Pharmacokinetics, and Preliminary Efficacy of Herbal Products for the Treatment of Acute Respiratory Viral Infections Including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Uganda; Phase 2A Open Label Clinical Trial	2023	ClinicalTrials.gov	https://clinicaltrials.gov/show/NCT05897203	Uganda
7	A dietary supplement for the management of patients with lumbar osteochondrosis	2021	ISRCTN	https://www.isrctn.com/ISRCTN17230715	Austria
8	Evaluation of the Effects of a Nutraceutical Composition Containing Derivatives From Natural Products on the Modulation of the Endocrine Neuroimmune Axis - Translational Study.	2021	ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT04810572	Brazil
9	A dietary supplement for semen parameters quality improvement in low sperm count and azoospermia patients	2020	ISRCTN	https://www.isrctn.com/ISRCTN15796121	Egypt
10	Pilot study on the effectiveness of selected natural products from traditional Iranian medicine sources (Bore armani and Raphanus niger Mill. combination/mixture) on the treatment of kidney stones	2020	IRCT	https://irct.behdasht.gov.ir/trial/49630	Iran

CTRI: Clinical Trials Registry – India; JPRN: Japan Primary Registries Network; ANZCTR: Australian New Zealand Clinical Trials Registry; ISRCTN: International Standard Randomized Controlled Trial Number; IRCT: Iranian Registry of Clinical Trials

The relevance of NPs in immunomodulation ideates from their multifaceted effects on immune cells, cytokines, and signaling pathways. These compounds can exert their immunomodulatory effects through various mechanisms, including:

Direct interaction with immune cells: NPs may directly bind to immune cell receptors or enzymes, thereby influencing their activation, proliferation, or differentiation. For example, certain plant-derived compounds can interact with TLRs or major histocompatibility complex (MHC) molecules, modulating antigen presentation and immune cell activation [101–104].

Regulation of cytokine production: Many NPs possess anti-inflammatory or pro-inflammatory properties by modulating the production and release of cytokines, which are key mediators of immune responses. NPs like *Echinacea* extract, curcumin, genistein, eugenol, 6-gingerol, thymoquinone, allicin, quercetin, betulinic acid, emodin, and parthenolide have shown pronounced effects on cytokine production and secretion in several physiological conditions [105–116].

Induction of regulatory immune responses: Some NPs have been shown to promote the generation of regulatory immune cells, such as regulatory T cells (Tregs) or M2 macrophages, which play critical roles in

maintaining immune homeostasis and tolerance [117–119]. By fostering a tolerogenic immune environment, these compounds may be beneficial for managing autoimmune diseases or preventing transplant rejection.

Modulation of immune cell trafficking: NPs can influence the migration and homing of immune cells to specific tissues or sites of inflammation through chemotactic effects or modulation of adhesion molecule expression [120, 121]. This can impact the intensity and duration of immune responses, shaping the overall immune landscape in various disease contexts.

Activation of immune cells

NPs can exert immunomodulatory effects by different mechanisms.

Immunostimulatory NPs can activate various immune cells, such as macrophages, dendritic cells, natural killer cells (NKs), T cells, and B cells, and increase the production and secretion of various cytokines, chemokines, and antibodies. It can also enhance the antigen presentation, phagocytosis, cytotoxicity, and proliferation of immune cells. They can be used for the prevention and treatment of infectious diseases, chronic inflammatory diseases, and immunodeficiency [122–125].

Immunosuppressive NPs can inhibit various immune cells, such as T cells, B cells, and mast cells, and decrease the production and secretion of various cytokines, chemokines, and antibodies. They can also inhibit the antigen presentation, activation, differentiation, and migration of immune cells. Such NPs can be used for the treatment of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, and allergic diseases, such as asthma, eczema, and anaphylaxis [126–129].

Dual-action compounds are NPs with both stimulatory and suppressive effects on immunity. They can modulate the immune system in a balanced and context-dependent manner, depending on the type, dose, and duration of exposure to the NP, and the status, phenotype, and function of the immune cells. It can regulate the immune system by affecting the expression and activity of various receptors, enzymes, transcription factors, and signaling molecules involved in immune regulation. Dual-action NPs can be used for the treatment of chronic inflammatory diseases, such as atherosclerosis, obesity, and neurodegeneration, and the enhancement of vaccine efficacy [105, 130]. Some of the NPs and their mode of action are described in Tables 1 and 2.

Synergistic effects of combining NPs with traditional anti-cancer treatments

NPs have demonstrated significant potential in enhancing the efficacy of traditional anti-cancer treatment strategies. Combining NPs with conventional therapies can result in synergistic effects, leading to improved treatment outcomes and reduced side effects. Several studies have highlighted the synergistic effects of NPs with chemotherapy agents. For example, the combination of curcumin, a bioactive compound derived from turmeric, with doxorubicin has been shown to enhance the cytotoxic effects on cancer cells and reduce drug resistance [131]. Similarly, resveratrol, found in grapes and red wine, has been reported to enhance the anti-cancer effects of paclitaxel in breast cancer cells [132].

NPs can also potentiate the effects of radiation therapy. For instance, epigallocatechin gallate (EGCG), a polyphenol found in green tea, has been shown to sensitize cancer cells to radiation, leading to increased apoptosis and reduced tumor growth. Co-treatment with EGCG and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), of highly aggressive colon cancer cells, synergistically increased cytotoxicity, by upregulation of death receptor 5 (DR5) and activation of caspase 8 demonstrating that EGCG can be a potent TRAIL sensitizer [133].

Synergistic effects of EGCG and L-theanine, which are key functional components of green tea, on nerve repair and regeneration can inhibit inflammation, promote metabolism, and nourish nerve cells, leading to potential benefits in the repair and regeneration of nerve cells. The combination of these compounds

promotes nerve cell health and slows down the progression of neurodegenerative diseases like Alzheimer's [134].

The synergistic effects observed when combining NPs with traditional anti-cancer treatments can be attributed to several mechanisms, including: enhanced cancer cell death: NPs can induce apoptosis and autophagy in cancer cells, thereby enhancing the cytotoxic effects of chemotherapy and radiation therapy and reducing the development of drug resistance to chemotherapy agents [135–137].

Understanding and harnessing the synergistic effects of combining NPs with traditional anti-cancer treatment strategies can lead to improved treatment outcomes and reduced side effects. Further research is needed to explore the optimal combinations, doses, and treatment schedules to maximize the synergistic effects and advance personalized cancer therapy.

The synergistic effects of natural compounds with conventional therapeutics against colorectal cancer progression and metastasis were well established [138]. Various in vitro and in vivo studies have shown that combining NPs with tamoxifen (TAM) results in synergistic anti-cancer effects. This combination enhances the inhibition of tumor cell growth, increases TAM sensitivity, and reduces the side effects or toxicity associated with TAM. However, some NPs, such as *Angelica sinensis* (Oliv.) Diels [Apiaceae], *Paeonia lactiflora* Pall., *Rehmannia glutinosa* (Gaertn.) DC., *Astragalus mongholicus* Bunge, and *Glycyrrhiza glabra* L. [Fabaceae], exhibit estrogen-like activity. This estrogenic activity might diminish the anti-cancer efficacy of TAM. On the other hand, certain NPs like morin, silybin, EGCG, myricetin, baicalein, curcumin, kaempferol, and quercetin have been found to enhance the bioavailability of TAM and its metabolites in vivo. Nevertheless, there is a lack of extensive clinical studies investigating the combined use of NPs and TAM [139].

The synergistic effects of the herbal mixture C5E in combination with the chemotherapeutic drug gemcitabine on the pancreatic cancer cell line PANC-1 notably decreased the SP cell percentage from 8.2% (control) to 5.1%, and more effectively induced early apoptosis compared to individual treatments. Additionally, the combination treatment led to a greater downregulation of sonic hedgehog mRNA expression, a protein associated with certain cancer types, compared to individual treatments [140].

The synergistic effects of *Clinacanthus nutans* Lindau (*C. nutans*) extracts when combined with gemcitabine, a conventional chemotherapy drug for pancreatic cancer. The research revealed that the non-polar stem extracts of *C. nutans* (SN extracts) synergistically enhanced the efficacy of gemcitabine, allowing for a dosage reduction of gemcitabine by 2.38 times to 5.28 times while maintaining its therapeutic effects. The combination treatment more effectively induced apoptosis in pancreatic ductal adenocarcinoma cells compared to either treatment alone, as indicated by the upregulation of Bax and downregulation of anti-apoptotic markers like Bcl-2, cIAP-2, and XIAP. The study concludes that although *C. nutans* extracts are not effective as a standalone cancer treatment, they can enhance the anti-tumor mechanism of gemcitabine [141].

In a study conducted by Kapadia et al. [142] (2013), *B. vulgaris* was co-administered with doxorubicin to pancreatic, breast, and prostate cancer cells. The combination of *B. vulgaris* and doxorubicin resulted in synergistic cytotoxic effects on pancreatic and breast cancer cells, but not on prostate cancer cells. This combined treatment approach with *B. vulgaris* has been reported to allow for a reduction in the dosage of anticancer drugs, thereby reducing adverse effects.

Collectively, these studies suggest that integrating NPs into cancer treatment protocols can enhance efficacy and reduce side effects, warranting further exploration to optimize treatment outcomes.

Role of NPs in managing tumor microenvironment

The potential of NPs to remodel the tumor microenvironment and overcome drug resistance in cancer immunotherapy by targeting and regulating immune cells, such as T cells, macrophages, and mast cells, as well as inflammatory cytokines within the tumor microenvironment has been well established [143].

Natural compounds function as metabolic modulators of the tumor microenvironment by modulating the metabolism of cells within the tumor microenvironment and their metabolic crosstalk as a promising strategy in anticancer therapies [144].

The study by Deng et al. [145] provides an overview of NPs and their derivatives as promising modulators of tumor immunotherapy. It discusses how these compounds can target various components of the immune system, including T cells, macrophages, B cells, NKs, Tregs, and myeloid-derived suppressor cells, and affect key pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), PI3K/Akt, mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)/signal transducers and activators of transcription (STAT). These studies suggest that NPs can enhance the therapeutic outcome of cancer immunotherapies by remodeling the tumor immunosuppressive microenvironment.

Precision medicine

Precision medicine represents an emerging approach in healthcare, aiming at tailored treatment solutions uniquely suited to each patient's genetic, molecular, and clinical makeup. This innovative approach holds promise for enhancing the diagnosis, prognosis, prevention, and treatment of a wide array of diseases, with a particular focus on immune-related disorders like diabetes, arthritis, atherosclerosis, cancer, autoimmune conditions, and allergies [146]. These disorders, characterized by complex and diverse manifestations, involve disruptions in the body's immune system, its crucial defense mechanism against external threats, and abnormal cellular activity [147, 148]. Through precision medicine, the underlying triggers and pathways of immune-related disorders can be differentiated, enabling the customization of treatment strategies to address individual patient needs effectively.

NPs and personalized medicine

Personalized therapy is one of the most promising applications of precision medicine in immune-related disorders. NPs can be used as potential sources of personalized immunotherapy, as they can target specific genes, proteins, and pathways involved in immune regulation, and induce specific immune responses against diseases. It plays a significant role in personalized immunotherapy, offering diverse compounds with potential therapeutic benefits in combating immune-related disorders. For example, EGCG from green tea has been found to inhibit certain immune checkpoint molecules, offering potential therapeutic benefits in cancer immunotherapy [149].

NPs can also be used as adjuvants, supplements, or delivery systems to enhance the efficacy and safety of immunotherapy. NPs can enhance the efficacy of immunotherapy when used as adjuvants or in combination with conventional treatments. Compounds like quercetin, found in fruits and vegetables, have been shown to improve the effectiveness of immunotherapy by sensitizing cancer cells to immune-mediated destruction [150, 151].

Many NPs exhibit minimal toxicity compared to synthetic drugs, making them attractive candidates for personalized immunotherapy. For example, compounds like apigenin, found in parsley and chamomile, have shown promising anti-inflammatory and immunomodulatory effects with few adverse reactions [152, 153].

Extensive preclinical and clinical investigations have explored the therapeutic potential of these compounds in personalized immunotherapy, shedding light on their efficacy, safety, and mechanisms of action in immune-related disorders [154]. Precision medicine emphasizes individualized treatment tailored to each patient's unique genetic, molecular, and clinical profiles. In the context of NPs, personalization can be based on, disease pathophysiology, multiomics-screening of biomarkers, the patient's age and health status, and interactions with other medications. However, recent advancements in genomic technologies have enabled rapid diagnosis and interpretation of genetic variations influencing therapy response, paving the way for targeted therapies that address specific disease features [155, 156]. Initiatives like the Human Genome and The Cancer Genome Atlas (TCGA) projects strive to elucidate the role of genetics and gene expression in disease progression and therapy response. These developments offer promise in

transforming drug discovery by leveraging genomic insights to identify new therapeutic targets and optimize treatment strategies. The "gene to screen" approach, focusing on genes as determinants of cellular phenotype, has emerged as a promising strategy in drug discovery, facilitating the identification of novel drug targets. Additionally, genome-wide association studies (GWAS) provide a cost-effective and unbiased method for identifying genetic determinants of diseases and elucidating underlying disease mechanisms [156, 157]. Through these approaches, the integration of NPs and genomic insights holds significant potential in driving innovative drug discovery and advancing personalized medicine.

Precision medicine and AI: revolutionizing personalized healthcare

Precision medicine tailors treatments to individual variations by identifying unique patient phenotypes. Artificial intelligence (AI) analyzes complex healthcare data to empower clinician decision-making and develop personalized treatment strategies. However, challenges like data integration, security, and bias exist. Successful AI adoption requires robust data governance, advanced analytics, and collaboration among healthcare professionals and data scientists. Despite challenges, AI's integration with precision medicine holds great promise for revolutionizing personalized healthcare and improving patient outcomes [158].

Clinical applications of NP-based therapy

NPs have gathered significant attention in clinical practice due to their diverse immunomodulatory properties and potential therapeutic benefits. For instance, curcumin has been studied for its ability to modulate immune responses, inhibit tumor growth, and enhance the efficacy of conventional cancer treatments [159–161]. EGCG, found in green tea, has been shown to inhibit immune checkpoint molecules, potentially improving the effectiveness of cancer immunotherapy [162, 163]. Compounds like quercetin, apigenin, and licorice extract have shown promising results in preclinical and clinical studies. Quercetin, abundant in fruits and vegetables, exhibits anti-inflammatory and immunomodulatory effects, making it a potential therapy for autoimmune conditions [72, 164]. Apigenin, found in parsley and chamomile, has demonstrated anti-inflammatory and immunosuppressive properties, suggesting its potential in autoimmune disease management [73, 165]. Licorice extract, containing glycyrrhizin, has been investigated for its immunomodulatory effects and potential therapeutic applications in autoimmune diseases [49, 166].

Challenges and considerations for clinical implementation

The clinical integration of NPs is promising but encounters numerous hurdles and factors to consider. These include grasping the intricate chemistry of herbal products and their formulation for therapeutic purposes in humans, ensuring the translation of fundamental scientific findings into clinical safety and effectiveness, establishing a framework for gathering evidence to validate traditional herbal medicines, and establishing a regulatory system that supports research funding and safeguards intellectual property rights. Additionally, there's a need to develop standard operating procedures for conducting clinical trials on herbal medicines. The integration of NPs into clinical practice offers promising opportunities for enhancing immune-related disorder management. However, addressing challenges such as standardization, safety concerns, regulatory approval, and patient education is essential for realizing the full potential of NP-based therapies in personalized medicine.

The journey from preliminary findings on the immunomodulatory capabilities of NPs to their formulation into evidence-based targeted therapeutics is fraught with challenges. A significant impediment is the lack of uniform research protocols to assess efficacy, safety, and action mechanisms, leading to inconsistent outcomes. Additionally, the inherent complexity and heterogeneity of NPs hinder the identification of specific bioactive constituents responsible for immunomodulatory actions, obscuring pharmacological profiles and optimal dosing. Further complicating the translation process is the incomplete understanding of the mechanisms of action in immunomodulation, necessitating detailed investigations to lay down a robust scientific groundwork. Moreover, navigating the intricate regulatory framework and ensuring stringent quality control are pivotal in the drug development process to guarantee safety, efficacy, and consistent quality. In summary, while the potential of NPs in immunomodulation is

promising, their development into targeted drugs requires meticulous research, standardization, and regulatory compliance for successful integration into evidence-based medicine [167–169].

NPs, continue to play a dominant role in modern drug development. Nobel laureate Youyou Tu's research on artemisinin [170] sparked renewed interest in traditional medicine and NPs, leading to groundbreaking developments such as the *Moringa oleifera* tablets for type 2 diabetes [171] and icariin softgels for HCC [172]. However, challenges persist, including issues with solubility, bioavailability, and stability, driving research in nanotechnology for novel dosage forms. Understanding drug targets is crucial for innovative drug discovery, particularly in the context of NPs which pose unique challenges in target identification.

The technological advancements in clinical research hold significant promise for revitalizing NP-based drug discovery across various domains. NPs have historically been used in combating infectious diseases, particularly as antibiotics. Leveraging cutting-edge techniques, such as harnessing the human microbiome for novel NPs, promises to unearth potent antimicrobial compounds. Given the pivotal role of gut microbiota in health, NP-based drug discovery targeting the gut microbiome emerges as a promising frontier [173, 174]. However, this area is still in its nascent stages, with many unanswered questions. Computational tools play a crucial role, in facilitating NP discovery through omics, chemical, and pharmacological analysis, as well as the integration of diverse datasets for NP-based drug discovery and development.

Conclusions

In conclusion, NPs persist as a fertile ground for discovering different formulations with diverse bioactivities, serving as both direct candidates for drug development and starting points for optimization into novel therapeutics for various diseases. Despite the ongoing challenges in drug development, NPs face additional hurdles related to accessibility, sustainable supply, and intellectual property constraints. However, scientific and technological progress lays a strong foundation for NP-based drug discovery to continue making significant steps in enhancing human health and longevity.

Abbreviations

AI: artificial intelligence

B. vulgaris: *Berberis vulgaris*

C. nutans: *Clinacanthus nutans*

EGCG: epigallocatechin gallate

HCC: hepatocellular carcinoma

NPs: natural products

TAM: tamoxifen

Declarations

Acknowledgments

We gratefully acknowledge the financial support provided by the Department of Health Research (DHR), Government of India, Women Scientist Scheme (File No.R.12013/21/2022-HR dated 30/03/2022), which enabled the completion of this review paper. Additionally, we extend our gratitude to the University of Kerala for its institutional support. We sincerely appreciate the resources and facilities provided by both institutions that contributed to the successful completion of this work.

Author contributions

MGP: Conceptualization, Writing—original draft, Writing—review & editing. HA: Writing—review & editing, Supervision. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This study was supported by Women Scientist Scheme, Department of Health Research (DHR), Ministry of Health & Family Welfare, Government of India [File No.R.12013/21/2022-HR]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Traditional medicine has a long history of contributing to conventional medicine and continues to hold promise [Internet]. WHO; c2024 [cited 2023 Apr 10]. Available from: https://www.who.int/news-room/feature-stories/detail/traditional-medicine-has-a-long-history-of-contributing-to-conventional-medicine-and-continues-to-hold-promise
2. Mukherjee PK, Bahadur S, Harwansh RK, Biswas S, Banerjee S. Paradigm shift in natural product research: traditional medicine inspired approaches. Phytochem Rev. 2017;16:803–26.
3. Sorokina M, Steinbeck C. Review on natural products databases: where to find data in 2020. J Cheminform. 2020;12:20.
4. Courdavault V, O'Connor SE, Jensen MK, Papon N. Metabolic engineering for plant natural products biosynthesis: new procedures, concrete achievements and remaining limits. Nat Prod Rep. 2021;38:2145–53.
5. Thomas DR, Goode PS, LaMaster K, Tennyson T. Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial. Adv Wound Care. 1998;11:273–6.
6. Montaner JS, Gill J, Singer J, Raboud J, Arseneau R, McLean BD, et al. Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease. J Acquir Immune Defic Syndr Hum Retrovirol. 1996;12:153–7.
7. Peng SY, Norman J, Curtin G, Corrier D, McDaniel HR, Busbee D. Decreased mortality of Norman murine sarcoma in mice treated with the immunomodulator, Acemannan. Mol Biother. 1991;3:79–87.
8. Roberts DB, Travis EL. Acemannan-containing wound dressing gel reduces radiation-induced skin reactions in C3H mice. Int J Radiat Oncol Biol Phys. 1995;32:1047–52.
9. Day MJ. Chapter 12 - Immunomodulatory therapy. In: Maddison JE, Page SW, Church DB, editors. Small Animal Clinical Pharmacology (Second Edition). Edinburgh: W.B. Saunders; 2008. pp. 270–86.

10. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, Pesta K, et al. Ashwagandha (*Withania somnifera*)—Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics. 2023;15:1057.
11. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. Altern Med Rev. 2000;5:334–46.
12. White PT, Subramanian C, Motiwala HF, Cohen MS. Natural Withanolides in the Treatment of Chronic Diseases. Adv Exp Med Biol. 2016;928:329–73.
13. Zhou R, Chen H, Chen J, Chen X, Wen Y, Xu L. Extract from *Astragalus membranaceus* inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway. BMC Complement Altern Med. 2018;18:83.
14. Phacharapiyangkul N, Wu LH, Lee WY, Kuo YH, Wu YJ, Liou HP, et al. The extracts of *Astragalus membranaceus* enhance chemosensitivity and reduce tumor indoleamine 2, 3-dioxygenase expression. Int J Med Sci. 2019;16:1107–15.
15. Liang Y, Chen B, Liang D, Quan X, Gu R, Meng Z, et al. Pharmacological Effects of Astragaloside IV: A Review. Molecules. 2023;28:6118.
16. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. Phytother Res. 2008;22:999–1012.
17. Reddi KK, Li H, Li W, Tetali SD. Berberine, A Phytoalkaloid, Inhibits Inflammatory Response Induced by LPS through NF-Kappaβ Pathway: Possible Involvement of the IKKα. Molecules. 2021;26:4733.
18. Xu X, Zhang L, Zhao Y, Xu B, Qin W, Yan Y, et al. Anti-inflammatory mechanism of berberine on lipopolysaccharide-induced IEC-18 models based on comparative transcriptomics. Mol Med Rep. 2020;22:5163–80.
19. Wang P, Li Q, Li K, Zhang X, Han Z, Wang J, et al. Betulinic acid exerts immunoregulation and anti-tumor effect on cervical carcinoma (U14) tumor-bearing mice. Pharmazie. 2012;67:733–9.
20. Szuster-Ciesielska A, Plewka K, Daniluk J, Kandefer-Szerszeń M. Betulin and betulinic acid attenuate ethanol-induced liver stellate cell activation by inhibiting reactive oxygen species (ROS), cytokine (TNF-α, TGF-β) production and by influencing intracellular signaling. Toxicology. 2011;280:152–63.
21. Viji V, Helen A, Luxmi VR. Betulinic acid inhibits endotoxin-stimulated phosphorylation cascade and pro-inflammatory prostaglandin E_2 production in human peripheral blood mononuclear cells. Br J Pharmacol. 2011;162:1291–303. Erratum in: Br J Pharmacol. 2021;178:2548.
22. Oliveira-Costa JF, Meira CS, Neves MVGD, Dos Reis BPZC, Soares MBP. Anti-Inflammatory Activities of Betulinic Acid: A Review. Front Pharmacol. 2022;13:883857.
23. Ammon HP. Boswellic Acids and Their Role in Chronic Inflammatory Diseases. Adv Exp Med Biol. 2016;928:291–327.
24. Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. Indian J Pharm Sci. 2011;73:255–61.
25. Singh S, Khajuria A, Taneja SC, Johri RK, Singh J, Qazi GN. Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders. Phytomedicine. 2008;15:400–7.
26. Efferth T, Oesch F. Anti-inflammatory and anti-cancer activities of frankincense: Targets, treatments and toxicities. Semin Cancer Biol. 2022;80:39–57.
27. Al-Yasiry AR, Kiczorowska B. Frankincense – therapeutic properties. Postepy Hig Med Dosw (Online). 2016;70:380–91.
28. Su S, Duan J, Chen T, Huang X, Shang E, Yu L, et al. Frankincense and myrrh suppress inflammation via regulation of the metabolic profiling and the MAPK signaling pathway. Sci Rep. 2015;5:13668. Erratum in: Sci Rep. 2015;5:15597.
29. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013;15:195–218.

30. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. Adv Exp Med Biol. 2007;595:1–75.
31. Fadus MC, Lau C, Bikhchandani J, Lynch HT. Curcumin: An age-old anti-inflammatory and anti-neoplastic agent. J Tradit Complement Med. 2016;7:339–46.
32. Payne A, Taka E, Adinew GM, Soliman KFA. Molecular Mechanisms of the Anti-Inflammatory Effects of Epigallocatechin 3-Gallate (EGCG) in LPS-Activated BV-2 Microglia Cells. Brain Sci. 2023;13:632.
33. Mokra D, Joskova M, Mokry J. Therapeutic Effects of Green Tea Polyphenol (−)-Epigallocatechin-3-Gallate (EGCG) in Relation to Molecular Pathways Controlling Inflammation, Oxidative Stress, and Apoptosis. Int J Mol Sci. 2022;24:340.
34. Mathema VB, Koh YS, Thakuri BC, Sillanpää M. Parthenolide, a sesquiterpene lactone, expresses multiple anti-cancer and anti-inflammatory activities. Inflammation. 2012;35:560–5.
35. Kwok BH, Koh B, Ndubuisi MI, Elofsson M, Crews CM. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IκB kinase. Chem Biol. 2001;8:759–66.
36. Percival SS. Aged Garlic Extract Modifies Human Immunity. J Nutr. 2016;146:433S–6S.
37. Nantz MP, Rowe CA, Muller CE, Creasy RA, Stanilka JM, Percival SS. Supplementation with aged garlic extract improves both NK and γδ-T cell function and reduces the severity of cold and flu symptoms: a randomized, double-blind, placebo-controlled nutrition intervention. Clin Nutr. 2012;31:337–44.
38. Bischoff-Kont I, Fürst R. Benefits of Ginger and Its Constituent 6-Shogaol in Inhibiting Inflammatory Processes. Pharmaceuticals (Basel). 2021;14:571.
39. Grzanna R, Lindmark L, Frondoza CG. Ginger—an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005;8:125–32.
40. Aouey B, Samet AM, Fetoui H, Simmonds MSJ, Bouaziz M. Anti-oxidant, anti-inflammatory, analgesic and antipyretic activities of grapevine leaf extract (*Vitis vinifera*) in mice and identification of its active constituents by LC-MS/MS analyses. Biomed Pharmacother. 2016;84:1088–98.
41. Di Lorenzo C, Sangiovanni E, Fumagalli M, Colombo E, Frigerio G, Colombo F, et al. Evaluation of the Anti-Inflammatory Activity of Raisins (*Vitis vinifera* L.) in Human Gastric Epithelial Cells: A Comparative Study. Int J Mol Sci. 2016;17:1156.
42. Thitimuta S, Pithayanukul P, Nithitanakool S, Bavovada R, Leanpolchareanchai J, Saparpakorn P. *Camellia sinensis* L. Extract and Its Potential Beneficial Effects in Antioxidant, Anti-Inflammatory, Anti-Hepatotoxic, and Anti-Tyrosinase Activities. Molecules. 2017;22:401.
43. Luo Q, Luo L, Zhao J, Wang Y, Luo H. Biological potential and mechanisms of Tea's bioactive compounds: An Updated review. J Adv Res. 2023;[Epub ahead of print].
44. Kamyab AA, Eshraghian A. Anti-Inflammatory, gastrointestinal and hepatoprotective effects of Ocimum sanctum Linn: an ancient remedy with new application. Inflamm Allergy Drug Targets. 2013;12:378–84.
45. Cohen MM. Tulsi - *Ocimum sanctum*: A herb for all reasons. J Ayurveda Integr Med. 2014;5:251–9.
46. Ng CY, Yen H, Hsiao HY, Su SC. Phytochemicals in Skin Cancer Prevention and Treatment: An Updated Review. Int J Mol Sci. 2018;19:941.
47. Leite CDS, Bonafé GA, Carvalho Santos J, Martinez CAR, Ortega MM, Ribeiro ML. The Anti-Inflammatory Properties of Licorice (*Glycyrrhiza glabra*)-Derived Compounds in Intestinal Disorders. Int J Mol Sci. 2022;23:4121.
48. Bisht D, Rashid M, Arya RKK, Kumar D, Chaudhary SK, Rana VS, et al. Revisiting liquorice (*Glycyrrhiza glabra* L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight. Phytomed Plus. 2022;2:100206.
49. Motawea MH, Abd Elmaksoud HA, Elharrif MG, Desoky AAE, Ibrahimi A. Evaluation of Anti-inflammatory and Antioxidant Profile of Oleuropein in Experimentally Induced Ulcerative Colitis. Int J Mol Cell Med. 2020;9:224–33.

50. Qabaha K, Al-Rimawi F, Qasem A, Naser SA. Oleuropein Is Responsible for the Major Anti-Inflammatory Effects of Olive Leaf Extract. J Med Food. 2018;21:302–5.
51. Mirsanei Z, Heidari N, Hazrati A, Asemani Y, Niknam B, Yousefi Z, et al. Oleuropein reduces LPS-induced inflammation via stimulating M2 macrophage polarization. Biomed Pharmacother. 2023; 163:114857.
52. Aghababaei F, Hadidi M. Recent Advances in Potential Health Benefits of Quercetin. Pharmaceuticals (Basel). 2023;16:1020.
53. Ferraz CR, Franciosi A, Emidio NB, Rasquel-Oliveira FS, Manchope MF, Carvalho TT, et al. Chapter 15 - Quercetin as an antiinflammatory analgesic. In: Mushtaq M, Anwar F, editors. A Centum of Valuable Plant Bioactives. Academic Press; 2021. pp. 319–47.
54. Hu HC, Lei YH, Zhang WH, Luo XQ. Antioxidant and Anti-inflammatory Properties of Resveratrol in Diabetic Nephropathy: A Systematic Review and Meta-analysis of Animal Studies. Front Pharmacol. 2022;13:841818.
55. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules. 2021;26:229.
56. Bernatoniene J, Jakstas V, Kopustinskiene DM. Phenolic Compounds of *Rhodiola rosea* L. as the Potential Alternative Therapy in the Treatment of Chronic Diseases. Int J Mol Sci. 2023;24:12293.
57. Wang S, Feng Y, Zheng L, He P, Tan J, Cai J, et al. Rosavin: Research Advances in Extraction and Synthesis, Pharmacological Activities and Therapeutic Effects on Diseases of the Characteristic Active Ingredients of *Rhodiola rosea* L. Molecules. 2023;28:7412.
58. Lee Y, Jung JC, Jang S, Kim J, Ali Z, Khan IA, et al. Anti-Inflammatory and Neuroprotective Effects of Constituents Isolated from *Rhodiola rosea*. Evid Based Complement Alternat Med. 2013;2013: 514049.
59. Trappoliere M, Caligiuri A, Schmid M, Bertolani C, Failli P, Vizzutti F, et al. Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells. J Hepatol. 2009;50:1102–11.
60. Tong WW, Zhang C, Hong T, Liu DH, Wang C, Li J, et al. Silibinin alleviates inflammation and induces apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes and has a therapeutic effect on arthritis in rats. Sci Rep. 2018;8:3241.
61. Huo CL, Wang B, Zhang X, Sun ZG. Skimmianine attenuates liver ischemia/reperfusion injury by regulating PI3K-AKT signaling pathway-mediated inflammation, apoptosis and oxidative stress. Sci Rep. 2023;13:18232.
62. Ratheesh M, Sindhu G, Helen A. Anti-inflammatory effect of quinoline alkaloid skimmianine isolated from *Ruta graveolens* L. Inflamm Res. 2013;62:367–76.
63. Ogunrinade FA, Iwuanyanwu VU, Sarker SD, Olajide OA. Neuroprotection by Skimmianine in Lipopolysaccharide-Activated BV-2 Microglia. Molecules. 2023;28:1317.
64. Kumar KS, Sabu V, Sindhu G, Rauf AA, Helen A. Isolation, identification and characterization of apigenin from *Justicia gendarussa* and its anti-inflammatory activity. Int Immunopharmacol. 2018; 59:157–67.
65. Kavitha SK, Viji V, Kripa K, Helen A. Protective effect of *Justicia gendarussa* Burm.f. on carrageenan-induced inflammation. J Nat Med. 2011;65:471–9.
66. Yoon JH, Kim MY, Cho JY. Apigenin: A Therapeutic Agent for Treatment of Skin Inflammatory Diseases and Cancer. Int J Mol Sci. 2023;24:1498.
67. Jang WY, Hwang JY, Cho JY. Ginsenosides from *Panax ginseng* as Key Modulators of NF-κB Signaling Are Powerful Anti-Inflammatory and Anticancer Agents. Int J Mol Sci. 2023;24:6119.
68. Yu T, Yang Y, Kwak YS, Song GG, Kim MY, Rhee MH, et al. Ginsenoside Rc from *Panax ginseng* exerts anti-inflammatory activity by targeting TANK-binding kinase 1/interferon regulatory factor-3 and p38/ATF-2. J Ginseng Res. 2017;41:127–33.

69. Saw CL, Wu Q, Kong AN. Anti-cancer and potential chemopreventive actions of ginseng by activating Nrf2 (NFE2L2) anti-oxidative stress/anti-inflammatory pathways. Chin Med. 2010;5:37.
70. Kang S, Min H. Ginseng, the 'Immunity Boost': The Effects of *Panax ginseng* on Immune System. J Ginseng Res. 2012;36:354–68.
71. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. Foods. 2017;6:92.
72. Shen P, Lin W, Deng X, Ba X, Han L, Chen Z, et al. Potential Implications of Quercetin in Autoimmune Diseases. Front Immunol. 2021;12:689044.
73. Kasiri N, Rahmati M, Ahmadi L, Eskandari N. The significant impact of apigenin on different aspects of autoimmune disease. Inflammopharmacology. 2018;26:1359–73.
74. Schueffler A, Anke T. Fungal natural products in research and development. Nat Prod Rep. 2014;31: 1425–48.
75. Singh AK, Rana HK, Pandey AK. Fungal-Derived Natural Product: Synthesis, Function, and Applications. In: Yadav AN, Singh S, Mishra S, Gupta A, editors. Recent Advancement in White Biotechnology Through Fungi: Volume 2: Perspective for Value-Added Products and Environments. Cham: Springer International Publishing; 2019. pp. 229–48.
76. Tan L, Song X, Ren Y, Wang M, Guo C, Guo D, et al. Anti-inflammatory effects of cordycepin: A review. Phytother Res. 2021;35:1284–97.
77. Zhang XL, Huang WM, Tang PC, Sun Y, Zhang X, Qiu L, et al. Anti-inflammatory and neuroprotective effects of natural cordycepin in rotenone-induced PD models through inhibiting Drp1-mediated mitochondrial fission. Neurotoxicology. 2021;84:1–13.
78. Zulhendri F, Lesmana R, Tandean S, Christoper A, Chandrasekaran K, Irsyam I, et al. Recent Update on the Anti-Inflammatory Activities of Propolis. Molecules. 2022;27:8473.
79. Hossain R, Quispe C, Khan RA, Saikat ASM, Ray P, Ongalbek D, et al. Propolis: An update on its chemistry and pharmacological applications. Chin Med. 2022;17:100.
80. Anauate MC, Torres LM, de Mello SB. Effect of isolated fractions of *Harpagophytum procumbens* D.C. (devil's claw) on COX-1, COX-2 activity and nitric oxide production on whole-blood assay. Phytother Res. 2010;24:1365–9.
81. Farpour HR, Rajabi N, Ebrahimi B. The Efficacy of *Harpagophytum procumbens* (Teltonal) in Patients with Knee Osteoarthritis: A Randomized Active-Controlled Clinical Trial. Evid Based Complement Alternat Med. 2021;2021:5596892.
82. Karkos PD, Leong SC, Karkos CD, Sivaji N, Assimakopoulos DA. *Spirulina* in clinical practice: evidence-based human applications. Evid Based Complement Alternat Med. 2011;2011:531053.
83. Calella P, Cerullo G, Di Dio M, Liguori F, Di Onofrio V, Gallè F, et al. Antioxidant, anti-inflammatory and immunomodulatory effects of spirulina in exercise and sport: A systematic review. Front Nutr. 2022;9:1048258.
84. Song SY, Park DH, Lee SH, Lim HK, Park JW, Jeong CR, et al. Purification of phenoloxidase from *Haliotis discus* hannai and its anti-inflammatory activity *in vitro*. Fish Shellfish Immunol. 2023;137: 108741.
85. Je JY, Park SY, Hwang JY, Ahn CB. Amino acid composition and *in vitro* antioxidant and cytoprotective activity of abalone viscera hydrolysate. J Funct Foods. 2015;16:94–103.
86. Li B, Lu F, Wei X, Zhao R. Fucoidan: structure and bioactivity. Molecules. 2008;13:1671–95.
87. Fitton JH, Stringer DN, Karpiniec SS. Therapies from Fucoidan: An Update. Mar Drugs. 2015;13: 5920–46.
88. Kohandel Z, Farkhondeh T, Aschner M, Pourbagher-Shahri AM, Samarghandian S. Anti-inflammatory action of astaxanthin and its use in the treatment of various diseases. Biomed Pharmacother. 2022; 145:112179.
89. Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. Mar Drugs. 2011;9:447–65.

90. Guan T, Ding LG, Lu BY, Guo JY, Wu MY, Tan ZQ, et al. Combined Administration of Curcumin and Chondroitin Sulfate Alleviates Cartilage Injury and Inflammation *via* NF-κB Pathway in Knee Osteoarthritis Rats. Front Pharmacol. 2022;13:882304.
91. Shavlovskaya OA, Zolotovskaya IA, Prokofyeva YS. Anti-inflammatory and anti-aging effects of chondroitin sulfate. Neurol, Neuropsychiatry, Psychosomatics. 2020;12:111–6. Russian.
92. Russell FD, Bürgin-Maunder CS. Distinguishing health benefits of eicosapentaenoic and docosahexaenoic acids. Mar Drugs. 2012;10:2535–59.
93. Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. Adv Nutr. 2012;3:1–7.
94. Claus-Desbonnet H, Nikly E, Nalbantova V, Karcheva-Bahchevanska D, Ivanova S, Pierre G, et al. Polysaccharides and Their Derivatives as Potential Antiviral Molecules. Viruses. 2022;14:426.
95. Chaisuwan W, Phimolsiripol Y, Chaiyaso T, Techapun C, Leksawasdi N, Jantanasakulwong K, et al. The Antiviral Activity of Bacterial, Fungal, and Algal Polysaccharides as Bioactive Ingredients: Potential Uses for Enhancing Immune Systems and Preventing Viruses. Front Nutr. 2021;8:772033.
96. Ahmed SA, Mendonca P, Elhag R, Soliman KFA. Anticancer Effects of Fucoxanthin through Cell Cycle Arrest, Apoptosis Induction, Angiogenesis Inhibition, and Autophagy Modulation. Int J Mol Sci. 2022; 23:16091.
97. Farzaneh Z, Vosough M, Agarwal T, Farzaneh M. Critical signaling pathways governing hepatocellular carcinoma behavior; small molecule-based approaches. Cancer Cell Int. 2021;21:208.
98. Chaudhry GE, Md Akim A, Sung YY, Sifzizul TMT. Cancer and apoptosis: The apoptotic activity of plant and marine natural products and their potential as targeted cancer therapeutics. Front Pharmacol. 2022;13:842376.
99. Sabu V, Krishnan S, Peter J, Aswathy IS, Lal Preethi SS, Simon M, et al. Synergistic effect of Betulinic acid, Apigenin and Skimmianine (BASk) in high cholesterol diet rabbit: Involvement of CD36-TLR2 signaling pathway. Cytokine. 2021;142:155475.
100. Shukla S, Bajpai VK, Kim M. Plants as potential sources of natural immunomodulators. Rev Environ Sci Biotechnol. 2014;13:17–33.
101. Paudel S, Mishra N, Agarwal R. Phytochemicals as Immunomodulatory Molecules in Cancer Therapeutics. Pharmaceuticals (Basel). 2023;16:1652.
102. Zhu H, Guo L, Yu D, Du X. New insights into immunomodulatory properties of lactic acid bacteria fermented herbal medicines. Front Microbiol. 2022;13:1073922.
103. Molteni M, Bosi A, Rossetti C. Natural Products with Toll-Like Receptor 4 Antagonist Activity. Int J Inflam. 2018;2018:2859135.
104. Bhaskar S, Sudhakaran PR, Helen A. Quercetin attenuates atherosclerotic inflammation and adhesion molecule expression by modulating TLR-NF-κB signaling pathway. Cell Immunol. 2016;310:131–40.
105. Sharma SM, Anderson M, Schoop SR, Hudson JB. Bactericidal and anti-inflammatory properties of a standardized *Echinacea* extract (Echinaforce®): dual actions against respiratory bacteria. Phytomedicine. 2010;17:563–8.
106. Cui YR, Bu ZQ, Yu HY, Yan LL, Feng J. Emodin attenuates inflammation and demyelination in experimental autoimmune encephalomyelitis. Neural Regen Res. 2023;18:1535–41.
107. Feng Y, Zhu X, Wang Q, Jiang Y, Shang H, Cui L, et al. Allicin enhances host pro-inflammatory immune responses and protects against acute murine malaria infection. Malar J. 2012;11:268.
108. Yücel Ç, Karatoprak GŞ, Açıkara ÖB, Akkol EK, Barak TH, Sobarzo-Sánchez E, et al. Immunomodulatory and anti-inflammatory therapeutic potential of gingerols and their nanoformulations. Front Pharmacol. 2022;13:902551.
109. Saadane A, Masters S, DiDonato J, Li J, Berger M. Parthenolide inhibits IκB kinase, NF-κB activation, and inflammatory response in cystic fibrosis cells and mice. Am J Respir Cell Mol Biol. 2007;36: 728–36.

110. Cai SQ, Tang ZM, Xiong C, Wu FF, Zhao JR, Zhang Q, et al. The anti-inflammatory effects of apigenin and genistein on the rat intestinal epithelial (IEC-6) cells with TNF-α stimulation in response to heat treatment. Curr Res Food Sci. 2022;5:918–26.
111. Goh YX, Jalil J, Lam KW, Husain K, Premakumar CM. Genistein: A Review on its Anti-Inflammatory Properties. Front Pharmacol. 2022;13:820969.
112. Khan FB, Singh P, Jamous YF, Ali SA, Abdullah, Uddin S, et al. Multifaceted Pharmacological Potentials of Curcumin, Genistein, and Tanshinone IIA through Proteomic Approaches: An In-Depth Review. Cancers (Basel). 2022;15:249.
113. Malik S, Singh A, Negi P, Kapoor VK. Thymoquinone: A small molecule from nature with high therapeutic potential. Drug Discov Today. 2021;26:2716–25.
114. Dudics S, Langan D, Meka RR, Venkatesha SH, Berman BM, Che CT, et al. Natural Products for the Treatment of Autoimmune Arthritis: Their Mechanisms of Action, Targeted Delivery, and Interplay with the Host Microbiome. Int J Mol Sci. 2018;19:2508.
115. Arulselvan P, Fard MT, Tan WS, Gothai S, Fakurazi S, Norhaizan ME, et al. Role of Antioxidants and Natural Products in Inflammation. Oxid Med Cell Longev. 2016;2016:5276130.
116. Barakat M, Syed NK, Hasen E, Abdulrazzaq SB, Thiab S, Al-Najjar MAA, et al. The effect of natural products on inflammatory cytokines production and secretion. Phytomed Plus. 2023;3:100488.
117. Chang Y, Zhai L, Peng J, Wu H, Bian Z, Xiao H. Phytochemicals as regulators of Th17/Treg balance in inflammatory bowel diseases. Biomed Pharmacother. 2021;141:111931.
118. Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018;9:17937–50.
119. Chen F, Gong M, Weng D, Jin Z, Han G, Yang Z, et al. Phellinus linteus activates Treg cells via FAK to promote M2 macrophage polarization in hepatocellular carcinoma. Cancer Immunol Immunother. 2024;73:18.
120. Wang K, Conlon M, Ren W, Chen BB, Bączek T. Natural Products as Targeted Modulators of the Immune System. J Immunol Res. 2018;2018:7862782.
121. Yousefpour P, Ni K, Irvine DJ. Targeted modulation of immune cells and tissues using engineered biomaterials. Nat Rev Bioeng. 2023;1:107–24.
122. Stroe AC, Oancea S. Immunostimulatory Potential of Natural Compounds and Extracts: A Review. Curr Nutr Food Sci. 2020;16:444–54.
123. Wagner H. Search for plant derived natural products with immunostimulatory activity: recent advances. Pure Appl Chem. 1990;63:1217–22.
124. Tandel RS, Dash P, Hussain Bhat RA, Thakuria D, Sawant PB, Pandey N, et al. Anti-oomycetes and immunostimulatory activity of natural plant extract compounds against *Saprolegnia* spp.: Molecular docking and *in-vitro* studies. Fish Shellfish Immunol. 2021;114:65–81.
125. Shahbazi S, Bolhassani A. Immunostimulants: types and functions. J Med Microbiol Infect Dis. 2016; 4:45–51.
126. Kumar S, Goel A, Padwad YS. Natural Products as Immunomodulatory and Chemosensitizing Agents in Colon Cancer Treatment. In: Vishvakarma NK, Nagaraju GP, Shukla D, editors. Colon Cancer Diagnosis and Therapy: Volume 2. Cham: Springer International Publishing; 2021. pp. 187–207.
127. Yin Y, Gong FY, Wu XX, Sun Y, Li YH, Chen T, et al. Anti-inflammatory and immunosuppressive effect of flavones isolated from *Artemisia vestita*. J Ethnopharmacol. 2008;120:1–6.
128. Mann J. Natural products as immunosuppressive agents. Nat Prod Rep. 2001;18:417–30.
129. Peter AE, Sandeep BV, Rao BG, Kalpana VL. Calming the Storm: Natural Immunosuppressants as Adjuvants to Target the Cytokine Storm in COVID-19. Front Pharmacol. 2021;11:583777.
130. Moudgil KD, Venkatesha SH. The Anti-Inflammatory and Immunomodulatory Activities of Natural Products to Control Autoimmune Inflammation. Int J Mol Sci. 2022;24:95.

131. Sen GS, Mohanty S, Hossain DMS, Bhattacharyya S, Banerjee S, Chakraborty J, et al. Curcumin enhances the efficacy of chemotherapy by tailoring p65NFκB-p300 cross-talk in favor of p53-p300 in breast cancer. J Biol Chem. 2011;286:42232–47.
132. Fukui M, Yamabe N, Zhu BT. Resveratrol attenuates the anticancer efficacy of paclitaxel in human breast cancer cells *in vitro* and *in vivo*. Eur J Cancer. 2010;46:1882–91.
133. Kwon OS, Jung JH, Shin EA, Park JE, Park WY, Kim SH. Epigallocatechin-3-Gallate Induces Apoptosis as a TRAIL Sensitizer via Activation of Caspase 8 and Death Receptor 5 in Human Colon Cancer Cells. Biomedicines. 2020;8:84.
134. Xie X, Wan J, Zheng X, Pan W, Yuan J, Hu B, et al. Synergistic effects of epigallocatechin gallate and l-theanine in nerve repair and regeneration by anti-amyloid damage, promoting metabolism, and nourishing nerve cells. Front Nutr. 2022;9:951415.
135. Al-Bari MAA, Ito Y, Ahmed S, Radwan N, Ahmed HS, Eid N. Targeting Autophagy with Natural Products as a Potential Therapeutic Approach for Cancer. Int J Mol Sci. 2021;22:9807.
136. Talib WH, Alsayed AR, Barakat M, Abu-Taha MI, Mahmod AI. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. Biomedicines. 2021;9:1353.
137. Nisar S, Masoodi T, Prabhu KS, Kuttikrishnan S, Zarif L, Khatoon S, et al. Natural products as chemo-radiation therapy sensitizers in cancers. Biomed Pharmacother. 2022;154:113610.
138. Liang Z, Xie H, Shen W, Shao L, Zeng L, Huang X, et al. The Synergism of Natural Compounds and Conventional Therapeutics against Colorectal Cancer Progression and Metastasis. Front Biosci (Landmark Ed). 2022;27:263.
139. Yen C, Zhao F, Yu Z, Zhu X, Li CG. Interactions Between Natural Products and Tamoxifen in Breast Cancer: A Comprehensive Literature Review. Front Pharmacol. 2022;13:847113.
140. Pak PJ, Lee DG, Sung JH, Jung SH, Han TY, Park SH, et al. Synergistic effect of the herbal mixture C5E on gemcitabine treatment in PANC-1 cells. Mol Med Rep. 2021;23:315.
141. Hii LW, Lim SE, Leong CO, Chin SY, Tan NP, Lai KS, et al. The synergism of *Clinacanthus nutans* Lindau extracts with gemcitabine: downregulation of anti-apoptotic markers in squamous pancreatic ductal adenocarcinoma. BMC Complement Altern Med. 2019;19:257.
142. Kapadia GJ, Rao GS, Ramachandran C, Iida A, Suzuki N, Tokuda H. Synergistic cytotoxicity of red beetroot (*Beta vulgaris* L.) extract with doxorubicin in human pancreatic, breast and prostate cancer cell lines. J Complement Integr Med. 2013;10:113–22.
143. Zhang W, Li S, Li C, Li T, Huang Y. Remodeling tumor microenvironment with natural products to overcome drug resistance. Front Immunol. 2022;13:1051998.
144. Dias AS, Helguero L, Almeida CR, Duarte IF. Natural Compounds as Metabolic Modulators of the Tumor Microenvironment. Molecules. 2021;26:3494.
145. Deng LJ, Qi M, Li N, Lei YH, Zhang DM, Chen JX. Natural products and their derivatives: Promising modulators of tumor immunotherapy. J Leukoc Biol. 2020;108:493–508.
146. Delhalle S, Bode SFN, Balling R, Ollert M, He FQ. A roadmap towards personalized immunology. NPJ Syst Biol Appl. 2018;4:9.
147. Nicholson LB. The immune system. Essays Biochem. 2016;60:275–301.
148. Chapter 19 - Autoimmune Diseases. In: Mak TW, Saunders ME, Jett BD, editors. Primer to the Immune Response (Second Edition). Boston: Academic Cell; 2014. pp. 517–52.
149. Almatroodi SA, Almatroudi A, Khan AA, Alhumaydhi FA, Alsahli MA, Rahmani AH. Potential Therapeutic Targets of Epigallocatechin Gallate (EGCG), the Most Abundant Catechin in Green Tea, and Its Role in the Therapy of Various Types of Cancer. Molecules. 2020;25:3146.
150. Kim JH, Kim MJ, Choi KC, Son J. Quercetin sensitizes pancreatic cancer cells to TRAIL-induced apoptosis through JNK-mediated cFLIP turnover. Int J Biochem Cell Biol. 2016;78:327–34.

151. Liskova A, Samec M, Koklesova L, Brockmueller A, Zhai K, Abdellatif B, et al. Flavonoids as an effective sensitizer for anti-cancer therapy: insights into multi-faceted mechanisms and applicability towards individualized patient profiles. EPMA J. 2021;12:155–76.
152. Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, et al. Natural Products as Anticancer Agents: Current Status and Future Perspectives. Molecules. 2022;27:8367.
153. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, et al. The Therapeutic Potential of Apigenin. Int J Mol Sci. 2019;20:1305.
154. Kumar S, Gautam V, Singh BP, Kumar D. Editorial: Investigating the impact of bioactive metabolites and extracts in human health and disease. Front Mol Biosci. 2023;10:1244316.
155. Strianese O, Rizzo F, Ciccarelli M, Galasso G, D'Agostino Y, Salvati A, et al. Precision and Personalized Medicine: How Genomic Approach Improves the Management of Cardiovascular and Neurodegenerative Disease. Genes (Basel). 2020;11:747.
156. Khoury MJ, Holt KE. The impact of genomics on precision public health: beyond the pandemic. Genome Med. 2021;13:67.
157. Debouck C. Integrating genomics across drug discovery and development. Toxicol Lett. 2009;186: 9–12.
158. Johnson KB, Wei WQ, Weeraratne D, Frisse ME, Misulis K, Rhee K, et al. Precision Medicine, AI, and the Future of Personalized Health Care. Clin Transl Sci. 2021;14:86–93.
159. Zhao C, Zhou X, Cao Z, Ye L, Cao Y, Pan J. Curcumin and analogues against head and neck cancer: From drug delivery to molecular mechanisms. Phytomedicine. 2023;119:154986.
160. Mundekkad D, Cho WC. Applications of Curcumin and Its Nanoforms in the Treatment of Cancer. Pharmaceutics. 2023;15:2223.
161. Luo F, Song X, Zhang Y, Chu Y. Low-dose curcumin leads to the inhibition of tumor growth via enhancing CTL-mediated antitumor immunity. Int Immunopharmacol. 2011;11:1234–40.
162. Rawangkan A, Wongsirisin P, Namiki K, Iida K, Kobayashi Y, Shimizu Y, et al. Green Tea Catechin Is an Alternative Immune Checkpoint Inhibitor that Inhibits PD-L1 Expression and Lung Tumor Growth. Molecules. 2018;23:2071.
163. Kciuk M, Alam M, Ali N, Rashid S, Głowacka P, Sundaraj R, et al. Epigallocatechin-3-Gallate Therapeutic Potential in Cancer: Mechanism of Action and Clinical Implications. Molecules. 2023;28: 5246.
164. Hosseinzade A, Sadeghi O, Naghdipour Biregani A, Soukhtehzari S, Brandt GS, Esmaillzadeh A. Immunomodulatory Effects of Flavonoids: Possible Induction of T CD4+ Regulatory Cells Through Suppression of mTOR Pathway Signaling Activity. Front Immunol. 2019;10:51.
165. Kang HK, Ecklund D, Liu M, Datta SK. Apigenin, a non-mutagenic dietary flavonoid, suppresses lupus by inhibiting autoantigen presentation for expansion of autoreactive Th1 and Th17 cells. Arthritis Res Ther. 2009;11:R59.
166. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. Phytother Res. 2018;32:2323–39.
167. Singh IP, Ahmad F, Chatterjee D, Bajpai R, Sengar N. Natural Products: Drug Discovery and Development. In: Poduri R, editor. Drug Discovery and Development: From Targets and Molecules to Medicines. Singapore: Springer Singapore; 2021. pp. 11–65.
168. Sarker SD, Nahar L. An introduction to natural products isolation. Methods Mol Biol. 2012;864:1–25.
169. Kellogg JJ, Paine MF, McCune JS, Oberlies NH, Cech NB. Selection and characterization of botanical natural products for research studies: a NaPDI center recommended approach. Nat Prod Rep. 2019; 36:1196–221.
170. Wang J, Xu C, Wong YK, Li Y, Liao F, Jiang T, et al. Artemisinin, the Magic Drug Discovered from Traditional Chinese Medicine. Eng. 2019;5:32–9.

171. Taweerutchana R, Lumlerdkij N, Vannasaeng S, Akarasereenont P, Sriwijitkamol A. Effect of *Moringa oleifera* Leaf Capsules on Glycemic Control in Therapy-Naïve Type 2 Diabetes Patients: A Randomized Placebo Controlled Study. Evid Based Complement Alternat Med. 2017;2017:6581390.
172. Liu Y, Yang H, Xiong J, Zhao J, Guo M, Chen J, et al. Icariin as an emerging candidate drug for anticancer treatment: Current status and perspective. Biomed Pharmacother. 2023;157:113991.
173. Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med. 2016; 375:2369–79.
174. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, et al. The gut microbiota and host health: a new clinical frontier. Gut. 2016;65:330–9.