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Review article

Phytoimmunomodulators: A review of natural modulators for complex immune system

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ABSTRACT

In the past few decades, the medicinal properties of plants and their effects on the human immune system are being studied extensively. Plants are an incredible source of traditional medicines that help cure various diseases, including altered immune mechanisms and are economical and benign compared to allopathic medicines. Reported data in written documents such as Traditional Chinese medicine, Indian Ayurvedic medicine support the supplementation of botanicals for immune defense reactions in the body and can lead to safe and effective immunity responses. Additionally, some botanicals are well-identified as magical herbal remedies because they act upon the pathogen directly and help boost the immunity of the host. Chemical compounds, also known as phytochemicals, obtained from these botanicals looked promising due to their effects on the human immune system by modulating the lymphocytes which subsequently reduce the chances of getting infected. This paper summarises most documented phytochemicals and how they act on the immune system, their properties and possible mechanisms, screening conventions, formulation guidelines, comparison with synthetic immunity-enhancers, marketed immunity-boosting products, and immune-booster role in the ongoing ghastly corona virus wave. However, it focuses mainly on plant metabolites as immunomodulators. In addition, it also sheds light on the current advancements and future possibilities in this field. From this thorough study, it can be stated that the plant-based secondary metabolites contribute significantly to immunity building and could prove to be valuable medicaments for the design and development of novel immunomodulators even for a pandemic like COVID-19.

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1. Introduction

There are several secondary metabolites, or phytochemicals, found in plants that can enhance human health by preventing and curing illnesses. Multiple diseases, both modern and ancient, cause an enormous number of deaths worldwide. Many people who are knowledgeable about the functioning of the immune system are working to maintain it. Although several businesses create synthetic medications that boost immune function, most people choose to maintain a healthy immune system naturally. Additionally, chronic

Abbreviations

ACE2	Angiotensin-converting enzyme 2
AKBA	Acetyl-11-keto-β-boswellic acid
AKT	Protein kinase B
AP-1	Activator protein
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
BAX	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
CD25	Cluster of differentiation 25
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CI	Chrysanthemum indicum
Cyt *c*	Cytochrome complex
DAMPs	Damage-associated molecular patterns
EGCG	Epigallocatechin-3-Gallate
HMGB1	High mobility group B1
HSP-20	Heat shock protein 20
HSP-27	Heat shock protein 27
IFN-β	Interferon-β
IFN-γ	Interferon gamma
IL-1	Interleukin 1
IL-12	Interleukin 12
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
IRAK	Interleukin Receptor-Associated Kinase
IκB	Inhibitor of kappa B
IκBα	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
Mcl-1	Myeloid cell leukemia-1
MHC	Major histocompatibility complex
MTND2	Mitochondrial NADH dehydrogenase subunit 2
mTOR	Mammalian target of rapamycin
MyD88	Myeloid differentiation primary response 88
NFÿB	Nuclear transcription factor Y subunit beta
NF-κB	Nuclear factor kappa B
NO	Nitric Oxide
NRF2	Nuclear factor-erythroid factor 2-related factor 2
p53	Tumor protein p53
PAMP	Pathogen-associated molecular pattern
PARP	Poly-ADP ribose polymerase
PHA	Polyhydroxyalkanoates
PKC	Protein Kinase C
PMA	Phorbol 12-myristate 13-acetate
PMBC	Peripheral blood mononuclear cells
RORγt	Retinoid-related orphan receptor gamma t
ROS	Reactive oxygen species
Sirt-1	Sirtuin-1
SOCS	Suppressor of cytokine signaling
Sp1	Stimulatory protein 1
SP-D	Surfactant protein D
Src	Proto-oncogene tyrosine-protein kinase
STAT3	Signal transducer and activator of transcription 3

usage of synthetic medications has been seen to reduce their effectiveness and may result in certain negative effects. Therefore, using botanicals is far better than taking allopathic medications. This has compelled researchers to look for botanical substitutes for these manmade medications. Plant metabolites enter the picture at that point. A lot of plant metabolites (phytochemicals) from ancient literature have been clinically tested for their ability to modulate the immune system. Herbal drugs improve a body's immunity naturally, without causing any side effects [1]. Rasayanas in Ayurveda and traditional Chinese medicines increase the body's natural resistance to fight against any foreign invasion. The human immune system is an intricate interaction of many dynamic cellular and molecular elements. Certain exogenous and endogenous variables generating pathophysiological circumstances modify the dynamically in immune "homeostasis." Immunomodulators can be used to control the pathophysiological states and return things to normal. The immune system's defenses against these diseases are strengthened by the immunomodulators' healing and renewing properties. These immunomodulators may act as immunostimulants, immunosuppressants, or immunoadjuvants to either stimulate or amplify the immunological response or to suppress the immune response. Due to the substantial toxicity or other adverse effects that are present in the majority of synthetic immunomodulators, plant-derived immunomodulators are being looked at as safer substitutes. Immunosuppressants can aid in the treatment of a variety of autoimmune and hypersensitivity conditions, whereas immunostimulants are used to treat cancer. A number of well-known plants, such as Acorus calamus, Actinidia macrosperma, Allium sativum, Alpinia galangal, Alternanthera tenella, Andrographis paniculata, Angelica sinensis, Argyreia speciosa, Azadirachta indica and many more are currently being investigated for their immunomodulatory potentials [1].

2. Immunity and immune system

Immunity is the ability of the body (Organisms/Humans) to recognize and resist toxic, unhealthy, infective/virulent, contagious microorganisms and also strengthen the body against these harmful organisms to prevent a number of diseases or infections and also the destruction of organs, tissues, and cells. Immune cells (mature immune stem cells) which circulate in every part of the body, are responsible for immunity.

The immune system is the body's defense system, which comprises many layers of security such as tissues, cells, etc., which protect the body from any foreign invasion. All three core components such as 1) the identification of pathogen insertion, 2) phagocytosis reaction, and 3) sparing the individual; the immune system works together to locate any foreign invasion of pathogens and eliminate them [2]. There are mainly two immune responses in the human body that show specific reactions against foreign bodies like germs and pathogens (Fig. 1). Among these responses, innate immunity (also called non-specific immune system) works as the primary defense system against a wide range of pathogens and adaptive immunity (known as acquired or specific immune system) develops over time and is responsible for defensive mechanisms against infections [3].

2.1. Immunomodulators and their categories

Immunomodulators are compounds that help in optimizing the immune response. Although the immune system is self-capable to produce cells that can recognize and eliminate any foreign invaders in the body, it can still become weak [4]. They are categorized into immunostimulants, immunoadjuvants, and immunosuppressants [3] (Fig. 2). Immunostimulants are generally non-specific and are considered to improve the resistance of a body to infection. They can function through both innate and adaptive immune responses. The immunostimulants are supposed to function as prophylactic agents and promoters in healthy individuals, i.e. as immuno-potentiators, by increasing the basic level of the immune response. They are supposed to act as immunotherapeutic agents in a person with an impaired immune response. Immunoadjuvants are used to increase vaccine effectiveness and are presumed as particular immune stimulants. Immunosuppressants are mainly used to cure autoimmune diseases and organ transplant rejection and are given in combination as in multidrug therapy [2].

3. Indian Ayurveda: Rasayanas

Ancient Scriptures like Atharva Veda, Charak Samhita, and Sushrut Samhita have mentioned plants to be used as medicines. Ayurveda is also known as a traditional Indian plant-based system of medicine and has been known for over 6000 years. Various plants with medicinal qualities, also called Rasayanas, are known to strengthen the human immune system and mental health [5]. Physicians in ancient times developed some therapeutic procedures that helped in rejuvenating all functions of the body. This is known as 'RasayanChikitsa' or rejuvenation therapy [6]. The Rasayana therapy enhances and enriches the quality of rasa with nutrients that help in anti-aging, attain long life, sharp memory, strong immune system to fight diseases, lustrous skin and complexion, development of sensory organs, etc. Triphala Rasayana, Chawanprash, and Brahma Rasayana are some of the very important Rasayanas mentioned in the Ayurveda [7]. There are some non-Rasayanic plants that exhibit activities that stimulate the immune system, fight pathogens, and

TLR4	Toll-like receptor 4
TNF	Tumour Necrosis Factor
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-α
TRAF4	TNF Receptor Associated Factor 4
TRAF6	TNF Receptor Associated Factor 6

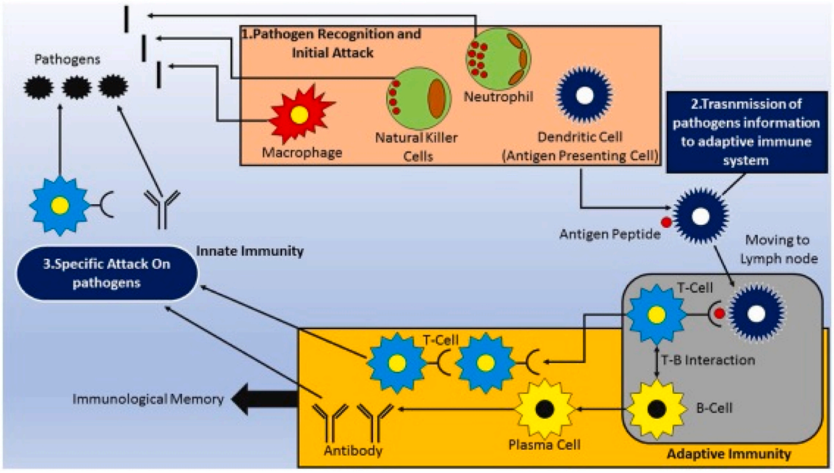

Fig. 1. Immune system overview: Innate immunity and adaptive immunity [3].

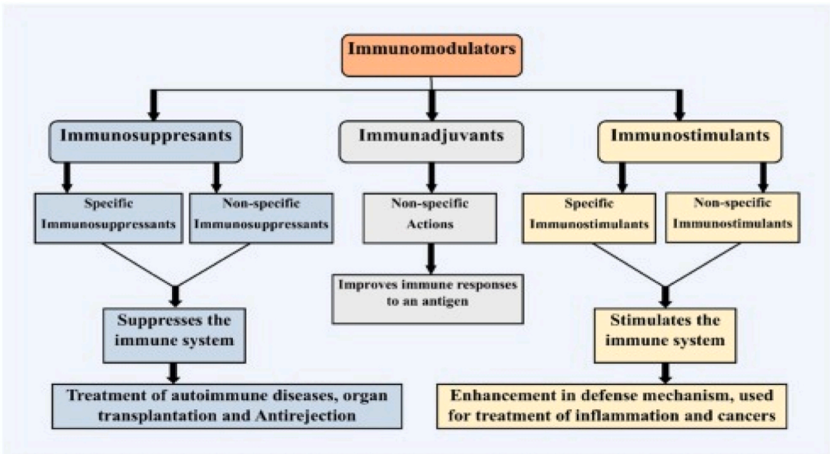

Fig. 2. Classified immune modulators with the mechanism of action [3].

have anti-inflammatory properties.

Rasayanas are of two types based on their needs. (1) KamyaRasayan: These types of Rasayanas are normal health promoters as they boost the energy level in the body and the immune system. Pranakamya, Medhakamya, and Srikamya are examples of Kamya Rasayana that promote vigor, endurance, brainpower, and skin tone, respectively. (2) NaimittikaRasayana: These types of Rasayanas help in fighting against specific diseases. This further is divided into two types which are based on the place of therapy: KutiPraveshikaRasayana (Indoor therapy) and VatatapikaRasayana (Outdoor therapy).

To undergo Rasayana therapy, one has to undergo detoxification or Samshodhana by the method of Panchkarma. These Rasayanas have more effect on the human body once the body is detoxified [7].

4. Traditional Chinese medicines

Traditional Chinese medicine is quite similar to Traditional Indian medicine or Ayurveda when it comes to functionality. They both act on the immune system of a human being, thereby improving general health rather than treating diseases. According to ancient philosophies, five elements constitute this materialistic world: Wood, Earth, Metal, Fire, and Water. They believed this world to be a single unit and that its movement gave rise to Yin and Yang, which means ‘opposites’. Yin and Yang are balanced by the four bodily senses of humor (qi, blood, moisture, and essence) and the internal organs of the body. For the body to function properly, the circulation, maintenance, and formation of these energies must be proper; otherwise, diseases develop.

Typically, traditional Chinese medicines have four types of drugs: principal drug, associate drug, adjuvant drug, and messenger drug. These are known as emperor, minister, assistant, and envoy in ancient Chinese literature. The history of ancient Chinese medicines which were first written can be traced back to the Eastern Han dynasty (AD25-AD220). A book entitled “Zhong Yao Da Ci

Dian" was published in 1977 (translated as a Chinese medical encyclopedia) and contains more than 5000 entries and with over 4000 substances obtained from plants and the rest from different sources like animals, minerals, etc.

Western medicines were later introduced to China by the Europeans. However, doctors in China practice traditional Chinese medicine along with modern treatment methods and equipment [8]. Several Chinese herbal plants (especially their secondary metabolites) like Radix Glycyrrhizae, Lentinusedodes, etc., modulate the immune response through different mechanisms like the proliferation of *tumor* cells; the prevention of viral replication; enhancement of antioxidant potential; raises antibodies number, etc. [9].

5. Phytoimmunomodulators: plant metabolites as immunomodulators

Secondary metabolites of plants have been identified to have unexpected, effective, significant, and engrossing applications with therapeutic potential to cure a vast range of infections, disorders, severe diseases, etc. These applications include a wide range of potentially beneficial and valuable actions i.e. antiviral, anti-aging, anti-tumor, antiprotozoal, anthelminthic, cholesterol-lowering as well as immunomodulatory activities. A number of well-known secondary metabolites are continuously being studied, elucidated, and explained for their remarkable and promising activities as shown in Table 1 [10].

Plants offer an abundance of secondary metabolites (also known as phytochemicals) having the ability to improve human health by preventing and treating diseases [11]. In the last few years, several plants and their metabolites are widely investigated and explored for their immunomodulating properties. The reason for this is to expand knowledge and awareness about the modulation of the immune system and to attain novel phytochemicals with unique targets and mechanisms. In the traditional system of medicine, numerous plant products i.e. metabolites, mediate its effects via direct action on pathogens as well as modulating immune response (by activating the host's natural and adaptive defense mechanisms). Thus, plant metabolites are responsible for boosting the immune response [12,13].

Several secondary metabolites are produced or synthesized by the plant which deals with a defensive mechanism or also essential physiological effects such as fascinating or repelling pollinators; barriers against phytophages; antimicrobial and responsible for the growth or development of lignified cell walls by providing structural components. Many pharma companies use these secondary metabolites as they act as a bioactive compound with their therapeutic effect on a specific site in patients and their compatible behavior in drug formulations, cosmeceuticals, and much more formulations. These features make the use of plant secondary metabolites incredible in both areas (scientific and industrial) [14]. Secondary metabolites are categorized into various groups (phenolics, flavonoids, alkaloids, terpenes, steroids, etc) according to their chemical structure (having sugar moiety or rings), their solubility in

Table 1
Plants with their bioactive moiety/phytoconstituents act as Immunomodulators.

Immunomodulators	Bioactive Moiety/Phytoconstituents
Polygonum cuspidatum	Polyphenols/Phenolics
Curcuma longa L.	Hydrocinnamic acid derivatives
Zingiber officinal	6-gingerol
Bidenspilosa	Centaurein
Boerhaavia diffusa	Eupalitin-3-*O*-β-D-galactopyranoside
Carica papaya	flavonoids (myricetin and Kaempferol)
Chrysanthemum indicum	Flavonoids
Hippophaerhamnoides	Flavones
Urticadioica	rutinoside
Reseda luteola	Luteolin
Terminalia chebula	Polyphenols
Camellia sinensis	Alkaloids
Cryptolepisdubia	Alkaloids
Hydrastis canadensis	Alkaloids
Piper longum	Piperine
Cichoriumintybus	Oligofructose
Gardenia jasminoides	Genipin
A. annua	Artemisinin
Elephantopusscaber	Elephantopin
Taxus brevifolia	Taxol
Tamarindus indica	polyphenols
Matricaria chamomilla	Heteropolysaccharides
Glycyrrhiza glabra	Polysaccharides
Asparagus racemosus	steroidal saponins
M. charantia	Momorcharin
Nigella sativa	Thymoquinone
Plantago species	glycosides
Mollugoverticillata	Triterpenoid
Mangifera indica	Mangiferin
Aloe vera	Dihydrocoumarin
Hypericum perforatum	terpene ketone
Andrographis paniculata	Andrographolide
Azadirachta indica	Nimbidin

different solvents, their biosynthetic pathway, and their composition (containing nitrogen or not) [15].

5.1. Polyphenols or phenolics

Polyphenols or phenolics are the substances that constitute one or more hydroxyl substituents in an aromatic ring, as well as functional derivatives (glycosides, esters, etc.). Polyphenols are considered to be the chief class of plant secondary metabolites that are synthesized from phenylalanine or tyrosine [16]. Polyphenols are further divided into various categories such as stilbenes (which comprises two aromatic rings) which are connected via a two-carbon bridge i.e. C6–C2–C6; hydrocinnamic acid derivatives; flavonoids; tannins.

5.1.1. Stilbene derivatives: resveratrol (trans-3,5,4′-trihydroxystilbene) from Polygonum cuspidatum [17]

Resveratrol, a natural polyphenol belongs to the stilbene class derived from many plants and it exerts its effects via modulating a variety of pathways. It has the potential to cross across the BBB and protect it (BBB integrity and permeability). This is evaluated by doing experiments on mouse models. In an experimental study using mouse models, resveratrol protects the BBB integrity and permeability by maintaining the functions of cerebral endothelial and by preventing the accumulation of beta-amyloids in the hippocampus. Resveratrol helps in neuroprotection by lowering the IL-1β (interleukin beta) in BV-2 murine microglial cells (Fig. 3). Resveratrol and its derivatives block the activation of microglial and decrease the formation of pro-inflammatory factors [18]. Th17 has molecular mechanisms that involve the homodimer Stat3, which is translocated into the nucleus after being acetylated and phosphorylated to activate transcription of the protein RORt, which then triggers transcription of the gene producing IL-17A. Sirtuin 1 (Sirt-1) is a NAD-dependent deacetylase that deacetylates proteins and stops the signaling cascade, allowing cells to differentiate and produce interleukin. Sirt-1 is activated by resveratrol, which causes Stat3 deacetylation and prevents it from migrating into the nucleus to stimulate target gene transcription (Fig. 3).

5.1.2. Hydrocinnamic acid derivatives: curcumin from Curcuma longa L. (Zingiberaceae)

C. longa, commonly known as turmeric, has numerous therapeutic uses. It has a compound known as curcumin which is derived from its rhizomes. It has properties like anti-inflammatory, anti-cancer, and wound healing capabilities [20]. Curcumin is the primary component of *C. longa* and has a remarkable immunomodulatory activity. After a lot of research, it has been proved that the administration of curcumin improves the bone marrow cellularity, phagocytic activity of macrophages, and alpha-esterase positive cells. Many other evidence indicates curcumin is capable of modulating both T cells proliferation and activation. Curcumin arrests cell proliferation (mediated by antibodies like PMA and anti-CD28 or mediated by PHA of T lymphocytes) [21]. A study confirmed that curcumin could block the production of Interleukin-2 and NF-κB; suppress the proliferation of mononuclear cells (present in human peripheral blood) [22]. Moreover, the administration of curcumin may potentially become a significant therapeutic compound for corona virus since it alleviates injuries to tissues after being infected with a virus, apoptosis, oxidative stress, and cytokine release syndrome. Fig. 4 shows the three possible mechanisms of curcumin through which it exerts its actions against COVID-19. Mechanism A shows the prevention of virus entry into the cells by disruption of the viral envelope, interaction with membrane proteins, and inhibition of viral proteases by the antiviral activity of curcumin against SARS-CoV-2; mechanism B shows the antiviral action of curcumin which regulates NRF2 (positive) and HMGB1 (negative); mechanism C Curcumin inhibits cytokine response syndrome and

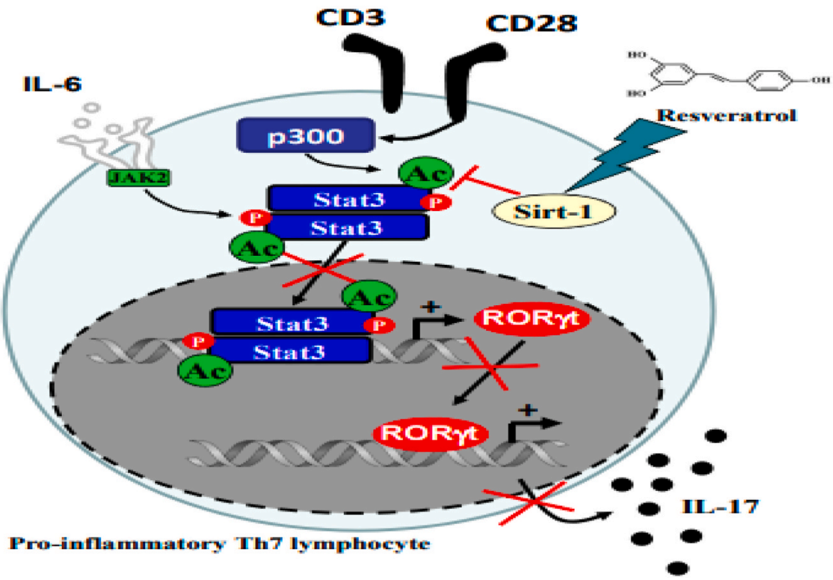

Fig. 3. Schematic molecular mechanisms of resveratrol with their targets [19].

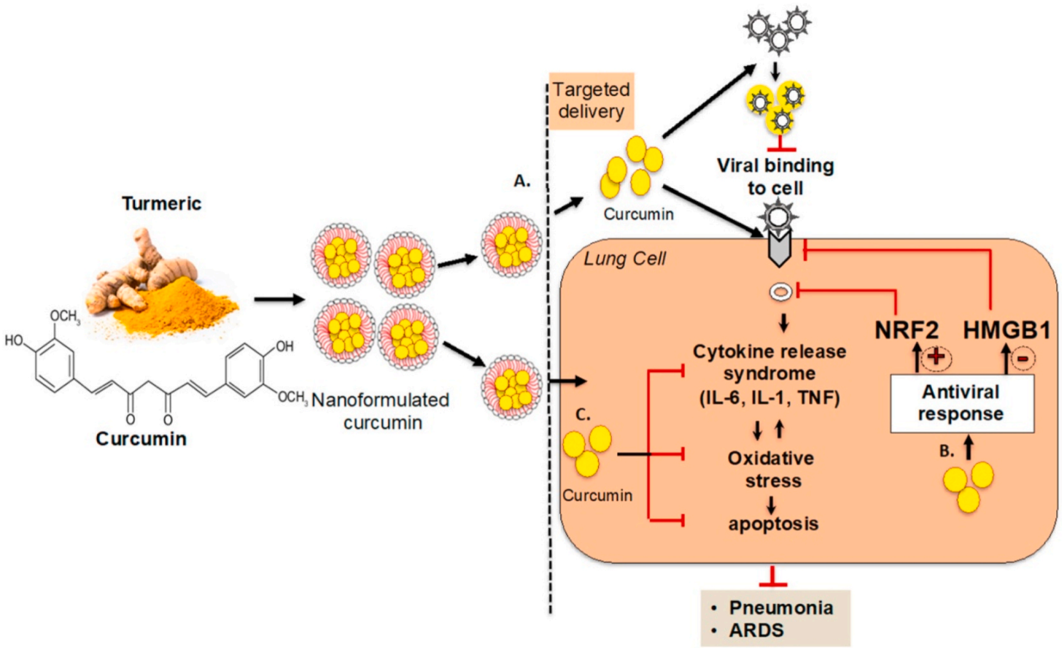

Fig. 4. Curcumin: potential mechanisms by which it may be effective against COVID-19 [23].

oxidative stress, mediating immunomodulatory responses and thereby preventing the progression of SARS-CoV-2 infection to pneumonia and/or ARDS.

5.1.3. 6-Gingerol from Zingiber officinale (Zingiberaceae)

Ginger (common name for *Zingiber officinale*) contains a highly pungent constituent called 6-gingerol. 6-gingerol has been identified to have anti-inflammatory, anti-bacterial, and anti-*tumor* properties. An experimental study (*in-vivo* and *in-vitro*) of 6-gingerol revealed that it is highly effective to treat *tumor*s and angiogenesis as well as angiogenesis-dependent disorders through different pathways like suppressing lung cells metastasis etc [24]. It exerts its action against inflammation with a different mechanism i.e. blockage of NF-kappa B and PKC signaling [25].

5.2. Flavonoids

5.2.1. Centaurein from Bidenspilosa (Asteraceae)

Records show that *Bidenspilosa* has been in use over the years as a traditional medicine in some countries as traditional medicine for treating bacterial infection and modulating the immune response. It is identified as the largest flower-bearing plant family in the world. Aqueous infusion of *B. pilosa* modulates the immune response through the enhancement of cytokine production and white blood cells (WBC) count. Two compounds centaurein (a flavonoid) and centaureidin (and its aglycone) extracted from butanol fraction *B. pilosa* and are responsible for the enhancement of the IFN-γ promoter function. Centaurein also helps enhancers like NFAT and NFκB work better (contained by IFN-γ promoter) [26].

5.2.2. Eupalitin-3-O-β-D-galactopyranoside from Boerhaavia diffusa (Nyctaginaceae)

B. diffusa is a plant that has widely been in use as a traditional medicine in India. It has been found to be potent and has significant immunomodulatory potential. Eupalitin-3-*O*-β-D-galactopyranoside of *B. diffusa* modulates the immune response by inhibiting PHA-stimulated mononuclear cells proliferation (cells present in peripheral blood), cell cytotoxicity along with NO production (lipopolysaccharide-induced). It also controls the formation of IL-2 (phytohemagglutinin stimulated) and TNF-α production (LPS stimulated) in human peripheral blood mononuclear cells (PBMCs) [27].

5.2.3. Myricetin from Carica papaya (Caricaceae)

Carica papaya constitutes two major flavonoids myricetin and Kaempferol. These flavonoids may be responsible for the immunomodulatory activity of *Carica papaya*. Its aerial parts (leaves, fruit) and seeds have been used to cure several ailments like cancer, acne [28].

5.2.4. Chrysanthemum indicum (Compositae)

C. indicum (CI), a traditional medicine, is widely used in the healing of inflammation, respiratory disorder, hypertension, and other disorders related to the immune system. In an experimental study, the immunomodulatory potential of CI extracts (mainly inflorescence or bud) was evaluated. The results of this study showed that plant (a butanol soluble fraction) has the potential to alter immune response may be due to flavonoids presence [29].

5.2.5. *Hippophaerhamnoides (Elaeagnaceae)*

The immunomodulatory activity of *Hippophaerhamnoides* (Seabuckthorn) has been evaluated by various *in-vivo* and *in-vitro* immunomodulatory models. A report revealed that flavones and ethanolic extracts of fruits of *H. rhamnoides* modulate the immune response by activating the production of interleukin-6 and TNF-alpha (present in peripheral blood mononuclear cells). Flavones are also responsible for the suppressed expression of CD25. *H. rhamnoides*(leaf extract) alters immune response via a cellular and humoral immune response [30].

5.2.6. *Quercetin-3-O-rutinoside and kaempferol-3-O-rutinoside from Urticadioica (Urticaceae)*

In Germany, *Urticadioica* has long been used as an adjuvant medicament for treating arthritis. Aerial parts like the leaves of this plant have major active flavonoids (Quercetin-3-*O*-rutinoside, kaempferol-3-*O*-rutinoside, and isorhamnetin-3-*O*-glucoside) which modulate the immune response through chemotaxis and intracellular killing action. They also reduce the number of inflammatory cytokines (like TNF-α) by inhibiting the genetic transcription factor and help in treating chronic granulomatous diseases [31].

5.2.7. *Luteolin from Reseda luteola*

Flavone (a subclass of flavonoids) consists of 3′,4′,5,7-tetrahydroxyflavone (Luteolin), and luteolin-7-glucoside (L7G, glycosylated form of luteolin). Flavones are the most abundant flavonoids present in aromatic plants as well as in various medicinal plants. Luteolin has antioxidant, anticarcinogenic, and immunomodulating properties. Due to its immunomodulating property, it has been used as an anti-inflammatory and anti-allergic agent [32]. *Reseda luteola* extract (which consists of a high amount of Luteolin), when applied topically resulted in reducing the inflammation (Fig. 5) its effectiveness was similar to hydrocortisone [33]. From these studies, it appears that luteolin has significant immunomodulatory potential. Another study reveals the luteolin's main pharmacological activity i.e. anti-inflammatory activity with mechanism i.e. Luteolin targets Src, Syk, and SOCS3 activated by cytokines, growth factors, and PAMPs linked to the activation of NF-κB, AP-1, and IRF-1, essential transcription factors to regulate inflammatory responses such as the release of cytokines, production of inflammatory mediates, and secretion of chemokines mentioned in Fig. 5 [34].

5.3. *Tannins*

5.3.1. *Terminalia chebula (Combretaceae)*

Fruits of *T. chebula* ('Myrobalan' or 'Haritaki') are a great source of tannins (polyphenols) with purgative, astringent, stomachic, and tonic properties. Despite these therapeutic uses, it is an ingredient in 'Triphala' (ayurvedic preparation). *Terminalia chebula*has been researched for its outcomes on the cell-mediated and humoral immune system in mice and resulted in an improvement in humoral antibody titer and delayed-type hypersensitivity in mice. From this, it is clear that *T. chebula* extracts exhibited immunostimulant properties [35].

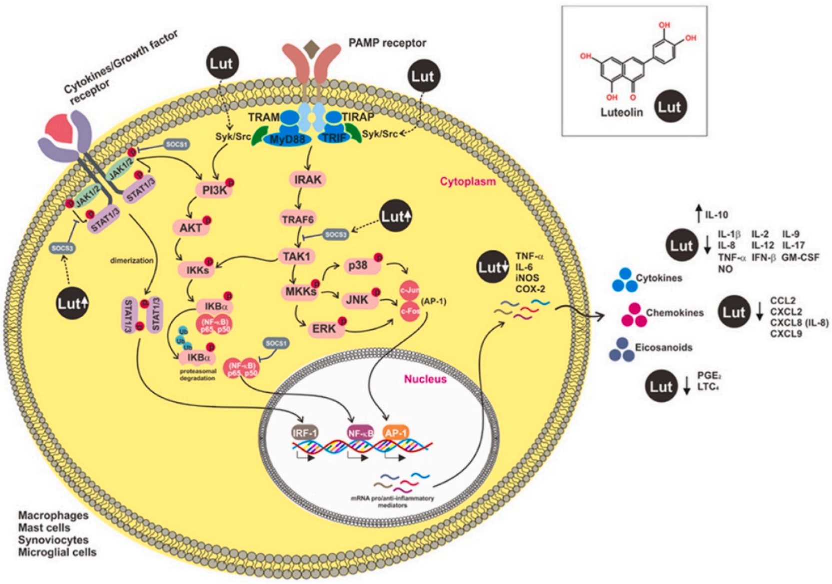

Fig. 5. Luteolin-targeted pathways involved in inflammatory signaling [34].

5.4. Alkaloids

5.4.1. Epigallocatechin-3-Gallate (EGCG) from Camellia sinensis (Theaceae)

Epigallocatechin-3-Gallate (EGCG) is an alkaloid derived from green tea (Camellia sinensis). It has been used for many decades as a traditional medicine due to its poly-pharmacological actions like anti-tumor, antiviral, and immunostimulatory properties in Vietnam and China. EGCG inhibits the development of TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (Aβ-induced microglial neuro-inflammatory response) and protects against neurotoxicity. In an experimental study on animals, EGCG treats animals suffering from neuroinflammation and memory loss. It acts by inhibiting astrocyte stimulation, and by reducing cytokine levels (TNF-α, IL-1β, IL-6) [36]. Additionally, in microglia cells, EGCG had anti-inflammatory activity. Such findings indicate that by inhibiting neuro-inflammatory biomarkers and reducing oxidative stress, the EGCG can prevent memory loss.

5.4.2. Buchananine from Cryptolepisdubia (Apocynaceae)

Buchananine an alkaloid is the chief active compound of C. buchanani (Syn: Cryptolepisdubia) [36]. In an experimental study on mice and rats, it has been found that C. buchanani (ethanol extract of the root) has immunomodulatory activity.

5.4.3. Berberine from Hydrastis canadensis (Ranunculaceae)

Berberine, an alkaloid, is derived from H. canadensis (Goldenseal). Hydrastis canadensis is native to North America and is widely adopted in the treatment of colds and flu along with echinacea. H. canadensis (root extract) was studied for its immunomodulatory activity on rats that were inserted with an innovative antigen (keyhole limpet hemocyanin) and results showed in-vivo immuno-modulatory potential(antigen-specific). It is thought that Berberine is an effective immunomodulator. In BALB/c mice, it suppressed experimental autoimmune tubulointerstitial nephritis. This induces a drop in the number of lymphocytes with CD3 (+), CD4 (+), CD8 (+), and sIg (+) compared with tubulointerstitial nephritis mice. The berberine also tends to reduce the amount of TNF-α, IFN-π, and nitric oxide in plasma but has not reduced the plasma amount of IL-12 in mice exposed to LPS [37]. In another study, berberine showed chondroprotective behavior via innate immunity through a specific mechanism which is shown in Fig. 6.

5.4.4. Tinospora cordifolia

Tinospora cordifolia exerts an immunomodulatory effect by stimulating tumor-associated macrophages. When *Tinospora cordifolia* extract is administered intraperitoneal in a mouse having a tumor it increases the phagocytosis ability of macrophages, antigen-presenting capability, and release of cytokines along with IL-1, TNF-α. T. cordifolia (Aqueous extract) can boost the phagocytic function of macrophages while the other extracts (aqueous and ethanolic) significantly improved antibody formation. And T. cordifolia (methanolic extract of the stem) exhibits an immunomodulatory effect by acting on humoral immunity by enhancing the plaque-forming cells (present in the spleen) and augmenting the activation of macrophages [39].

5.4.5. Piperine from Piper longum (Piperaceae)

Piper longum is a traditional medicine used in Asia and the Pacific Islands, particularly in Indian medicine. Piper longum has many medicinal properties. It is reported as significant potential for treating sexually transmitted diseases like gonorrhea, pain during menstruation, tuberculosis, sleeping disturbances, and respiratory tract infections [39]. Piperine (an alkaloid presents in Piper longum) and alcoholic extract of P. longum fruits were studied for their immunomodulatory property. The results revealed that the piperine and extract affect the immune system by increasing the number of WBC and by protecting the cellularity of bone marrow as well as enhancing α-esterase positive cells count, antibody production, and an overall count of plaque-forming cells.

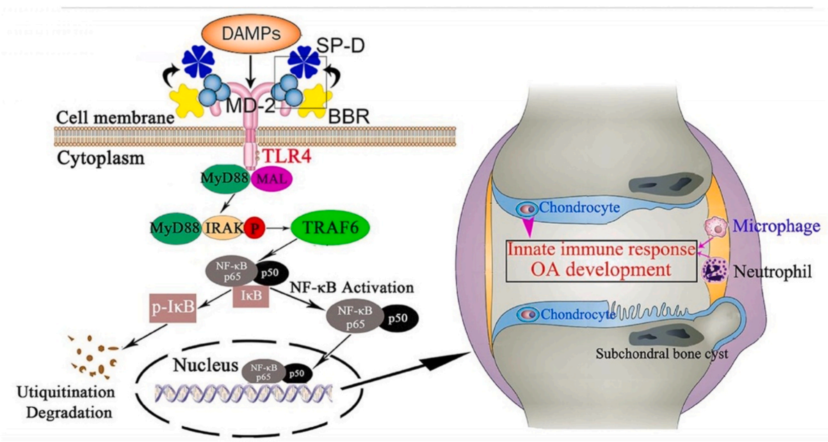

Fig. 6. Putative chondroprotective mechanism of berberine via innate immunity [38].

5.5. Carbohydrates

5.5.1. Oligofructose and inulin from Cichoriumintybus (Asteraceae)

Cichoriumintybus contains two fractions namely Oligofructose and inulin which modulates the immune response by enhancing the growth rate of bifidobacterial (beneficial strain present in the colon) [40]. An investigational study demonstrated that *C. intybus* (70 % ethanol extract) exhibited immunomodulatory activity by completely blocking the proliferation of lymphocytes in the presence of phytohemagglutinin [41].

5.6. Terpenes/terpenoids

5.6.1. Monoterpenoids

5.6.1.1. Genipin, (the aglycone of geniposide) from Gardenia jasminoides. Genipin., an ingredient of the fruits of *Gardenia jasminoides* has the potential to modulate the immune response by inhibiting NF-κB and iNOS expression. Traditional medicines have incorporated the fruit of *Gardenia jasminoides* Ellis (Rubiaceae) to treat inflammation, jaundice, headaches, edoema, fever, hepatic diseases, and hypertension. Effective pharmacological properties have been shown to include cytotoxic, anti-inflammatory, fibrolytic, and protective activity against oxidative damage [42].

5.6.1.2. Limonene. Limonene, a monoterpene, helps in the suppression of NF-κB activation. Here, the study examined at how the monoterpenes affect nuclear factor-κB (NF-κB), a calcium-dependent transcription factor essential for WEHI-231 B-lymphoma cells to survive. In contrast to other monoterpenes, perillyl alcohol short-term administration caused calcium levels to drop steadily as opposed to the transitory effects other monoterpenes generated. Treatment with perillyl alcohol also quickly caused decreases in target gene induction and NF–B DNA-binding activity, which were linked to an increase in apoptosis in these B-lymphoma cells [43].

5.6.2. Sesquiterpenoids

5.6.2.1. Artemisinin from A. annua. Leaves of *A. annua* (a traditional Chinese medicinal plant) were used to extract Artemisinin [44]. It has been used to treat multidrug-resistant malaria as an effective antimalarial drug that also possesses properties like antifungal, anticancer (Fig. 7), anti-angiogenic, and immunosuppressive [45].

5.6.2.2. Elephantopin derivatives from Elephantopusscaber. Isodeoxyelephantopin and deoxyelephantopin, sesquiterpene lactones, are the derivatives of the *Elephantopusscaber* plant [47]. These two novel sesquiterpene lactones have been possessing anti-inflammatory activities as well as anti-cancer activities by suppressing the activation of NF-κB [48].

5.6.3. Diterpenoids

5.6.3.1. Taxol from Taxus brevifolia. Taxol also known as Paclitaxel, is a complex polyoxygenated diterpenoid derived from the bark of Taxus brevifolia (Pacific yew tree). Taxol is an extremely significant anti-cancerous drug (specifically against breast cancer) [49]. Paclitaxel exhibits immunomodulatory activity against tumors and controls the activation of lymphocytes [50].

5.6.3.2. Tanshinone IIA from Salvia miltiorrhiza. Tanshinone IIA is the primary bioactive diterpene quinone from Salvia miltiorrhiza

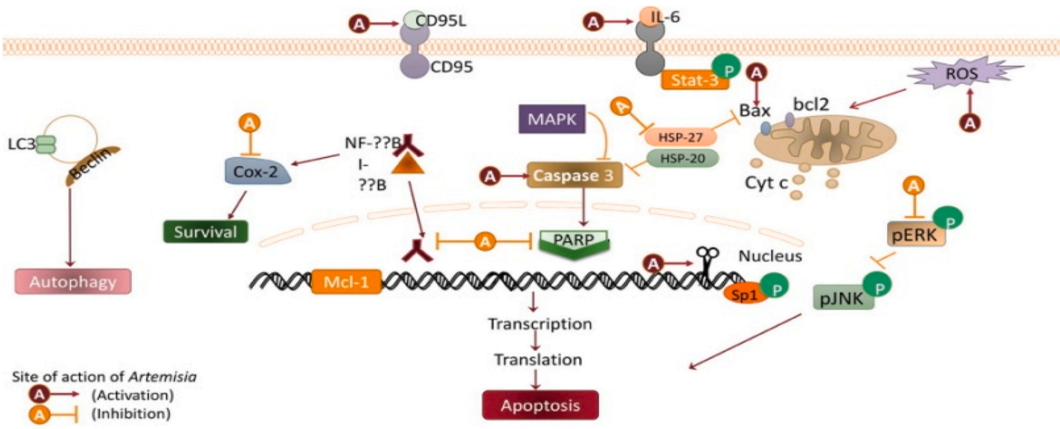

Fig. 7. Pathway: Molecular targets of Artemisia in cancer cells [46].

rhizomes (a common herb of TCM). It is effective in the treatment of several inflammatory and immunological disorders as well as coronary heart diseases and breast cancer. Tanshinone IIA also has cytotoxic activity by inhibiting DNA synthesis and cancer cell proliferation, regulating gene expression, differentiation, and apoptosis, inhibiting the telomerase activity of cancer cells, and altering the expression of cell surface antigens. Tanshinone IIA can impede NF-πB signals and inflammatory mediators [51–53]. The Tan-IIA imidazole derivative TA25 was found to specifically bind and stabilize c-myc G-quadruplex DNA, causing DNA damage and increasing the formation of reactive oxygen species (ROS), which suppressed lung cancer A549 cell proliferation, migration, and invasion. TA25 was found to modulate the PI3K/Akt/mTOR signaling pathway, causing tumor cells to enter S-phase. To put it another way, TA25 could become a viable lung cancer inhibitor (Fig. 8).

5.6.3.3. Carnosol and carnosic acid from rosemary extracts (Rosmarinus officinalis). Carnosol and carnosic acid are abietane-type diterpenoids derived from Rosemary extracts (*Rosmarinus officinalis*) [54]. These compounds have significant anti-inflammatory and antioxidant potential through the initiation of Nrf-2-activated HO-1 expression and preventing the activation of NF-κB signaling [54,55].

5.6.3.4. 6-Hydroxy-5,6-dehydrosugiol from Cryptomeria japonica. It has been reported that 6-hydroxy-5,6-dehydrosugiol (HDHS), a novel abietane-type diterpenoid derived from the stem bark of *Cryptomeria japonica* has the potential to modulate the immune response by suppressing *tumor* development (in prostate cancer) [56].

5.6.4. Triterpenoids

5.6.4.1. Celastrol from Celastrusregelii(Celastraceae). Celastrol is a pentacyclic triterpenoid that is extracted from the "Thunder of God Vine" (a popular Chinese herb) [57]. Studies reveal that it has strong antioxidant, anti-inflammatory, neuroprotective and anti-*tumor* activities. Celastrol can inhibit inflammation and tumor growth by suppressing NF-πB [58,59].

5.6.4.2. Boswellic acid from Boswellia serrata (Burseraceae). Boswellia serrata (also known as Salai), is used to treat rheumatoid arthritis, back pain, fibrositis, and osteoarthritis as well as anti-inflammatory and pain-relieving effects. Boswellic acid (a pentacyclic triterpene acid) is extracted from the gum resin of *B. serrata*. Boswellic acid has the potential to modulate cell-mediated and humoral immunity [60]. An experimental study showed anti-anaphylactic activity and mast cell stabilization activity of Boswellic acid [60,61]. A research study on mice brain cells by using acetyl-11-keto-β-boswellic acid (AKBA), described the neuroprotective effect of AKBA by protecting neurons against oxidative stress and inflammation in Alzheimer's disease and this effect involves the Nrf2/HO-1 and nuclear factor-kappa B signaling pathways as shown in Fig. 9 [62].

5.6.4.3. Ursolic acid from rosemary. Ursolic acid, a pentacyclic triterpene; is the non-toxic and primary active compound of some traditional herbal medications, such as leaves of rosemary. It has been recognized that it has anti-inflammatory and anticancer properties [63]. It has been reported that ursolic acid has immunomodulatory activity [64].

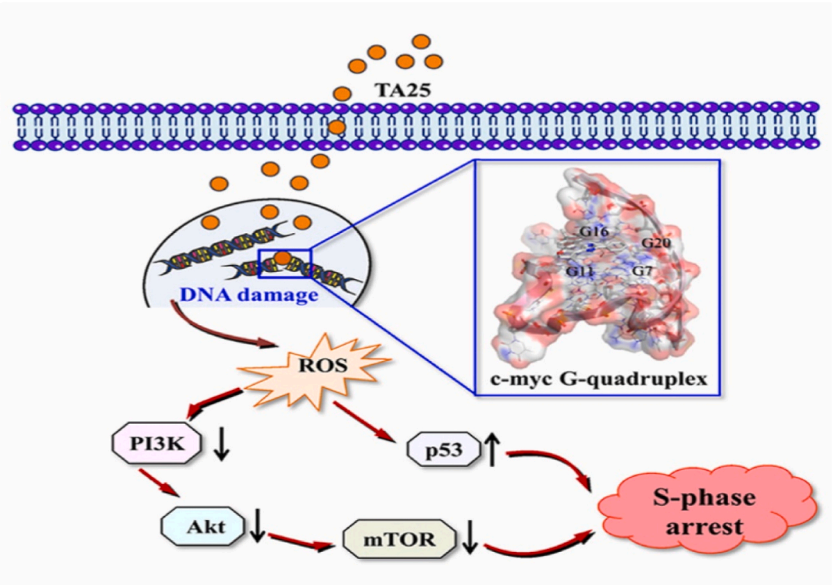

Fig. 8. Mechanism of blockage of lung cancer progression [53].

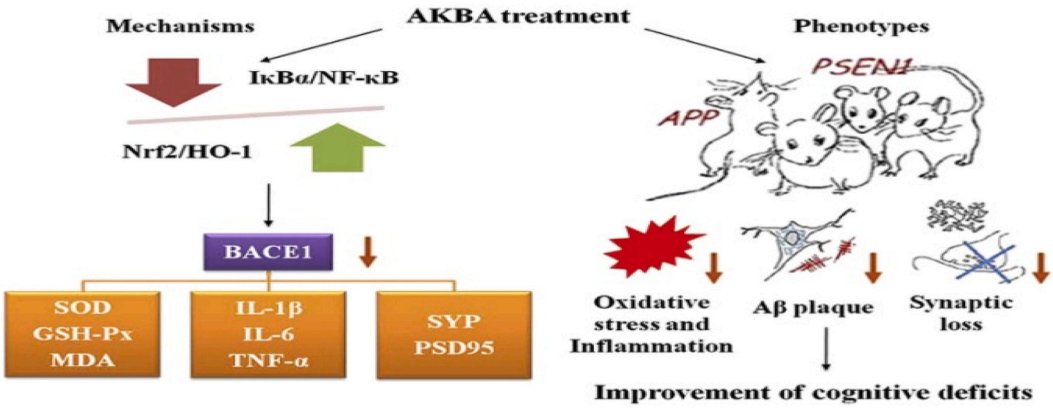

Fig. 9. Neuroprotective effect of acetyl-11-keto-β-boswellic acid [62].

5.6.4.4. Betulinic acid from white birch tree. Betulinic acid and its derivatives (lupane-type triterpenoids), were known to have the potential to fight pathogen infections, cancer, immunomodulation action, and diverse sorts of inflammation [65,66]. This anticancer activity was related to its ability to directly cause permeabilization of the mitochondrial membrane, a primary step that seals the fate of the cell during the apoptotic process [65]. It has also been found that betulinic acid acted as a deactivator of IKKα and NF-κB [66]. The research revealed that betulinic acid possesses activity against SARS-CoV [67].

5.6.4.5. Lupeol. Lupeol has a chemical structure similar to betulinic acid [54]; has plenty of pharmacological activities and further investigated therapeutic implications for some specific cancers [68] and inflammatory conditions [69]. Recent studies showed that lupeol modulates the expression of several molecules, such as cytokines IL-2, IL4, ILβ, proteases, α-glucosidase, cFLIP and Bcl-2 [68]. It inhibits NF-Kb signaling through a process known as phosphorylation i.e. it causes phosphorylation of IκBα protein. Lupeol may also suppress supplementary signaling pathways, like the Akt-dependent, which can lead to its several anti-inflammatories and anti-cancer properties shown in Fig. 10 [69,70].

5.6.5. Carotenoids

Such antioxidant-exhibiting carotenoids will trigger potential development as immunomodulators.

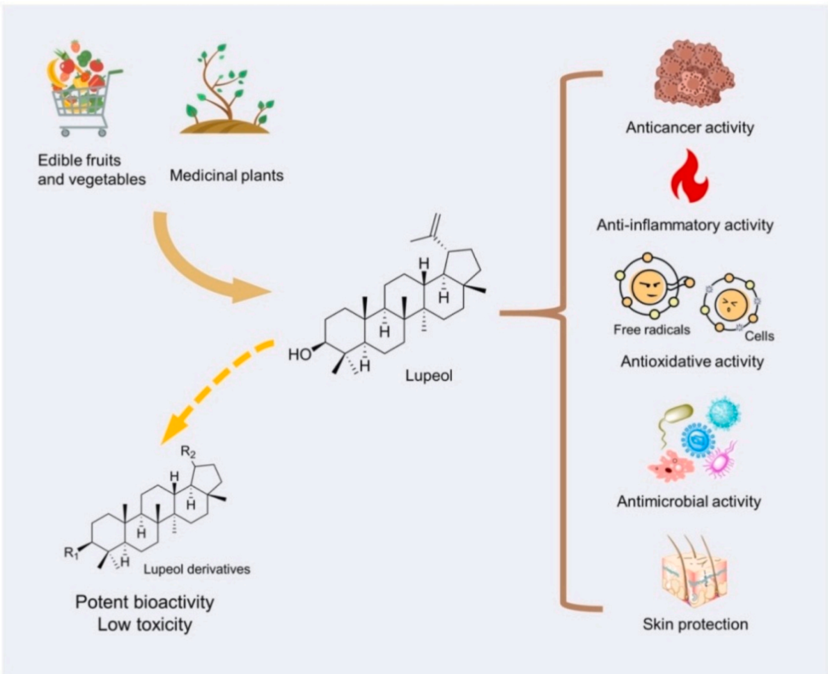

Fig. 10. Various potent activities of lupeol [71].

5.6.5.1. Lutein from β-Carotene. β-Carotene is the most frequent cyclic tetraterpene and also the most active naturally occurring pro-vitamin A which is converted to vitamin A [55]. The lipophilic carotenoid xanthophyll, lutein, is a dihydroxy derivative of β-carotene. Modulating skin reaction to UVR may protect against the deleterious effects of solar radiation. It can also guard against oxidative stress and prevention of age-related macular deterioration and it also possesses neuroprotective action i.e. it inhibits neural retinal damage in retinal swelling [72,73].

5.6.5.2. Lycopene. The most popular carotenoid found in the body of a human being is lycopene, an acyclic tetraterpene that is derived from vegetables (mostly red) and fruits. Lycopene is a potent antioxidant, more active than vitamin E and hence, can withstand free radical cell attack during oxidative stress. The prevalence of various chronic diseases has also been reported to be reduced, such as cardiovascular disorders, rheumatoid arthritis, and atherosclerosis [55,70].

5.6.6. Other terpenoids

*5.6.6.1. Nimbidin from Azadirachta indica (Meliaceae). A. indica*is an evergreen and prominent medicinal plant with many promising biological activities for instance anti-inflammatory, anti-diabetic, antiviral, anticarcinogenic, immunostimulatory, etc. Nimbidin (tetranortriterpenes mixture) is the chief active compound of *A. Indica* seed oil. It altered the immune response to treat inflammation and arthritis problems by significantly inhibiting the functions of macrophages and neutrophils. Nimbidin also affects the production level of nitric oxide (NO) and prostaglandin E2 (PGE2) levels i.e. reduce them in macrophages (lipopolysaccharide (LPS) stimulated). In observation, it is reported nimbidin is responsible for diminished degranulation in neutrophils like β-glucuronidase, myeloperoxidase, and lysozyme [74,75].

5.6.6.2. Asiaticoside from Centellaasiatica (Umbelliferae). Centella asiatica ('mandukparni') is a well-known plant having various significant medicinal uses such as spasmolytic, sedative, anti-stress, and anti-anxiety action. Asiaticoside, a terpene, is the chief compound *C. asiatica*. It was found in a study that extracts and asiaticoside of *C. asiatica* hold immunomodulatory potential through enhancement of phagocytic index and the total number of WBC. Water extract of *C. asiatica* stimulates proliferation and the formation of cytokines while ethanol extract of *C. asiatica* inhibits mitogenesis and the formation of cytokines [76].

5.6.6.3. Andrographolide, 14-deoxyandrographolide and 14-deoxy-11, 12-didehydroandrographolide from Andrographis paniculata (Acanthaceae). Andrographis paniculata has the potential to treat a number of diseases such as cold, diarrhea, fever and inflammation, etc. It is a Chinese and Indian herb that consists of diterpene compounds andrographolide,14-deoxyandrographolide, and 14-deoxy-11, 12-didehydroandrographolide. These compounds exhibit a significant immunomodulatory activity. They modulate the immune response by inducing interleukin-2 (IL-2) and increase proliferation as well as causes inhibition of nitric oxide in macrophages (endotoxin stimulated) [77,78].

5.6.6.4. Hyperforin from Hypericum perforatum (Hypericaceae). Hyperforin (a cyclic terpene ketone) [79] is the chief active compound of the *Hypericum perforatum* (St. John's wort).*H. perforatum* has been used as an ancient folk remedy due to its antiviral, antibacterial, anti-inflammatory activities and it treats a number of diseases like bruises, dysentery, jaundice, diarrhea, an antidepressant. *H. perforatum* extract modulates immune response through the degradation of human peripheral blood mononuclear cells and alters the formation of the neopterin. The immunosuppressing effect is exerted by a lipophilic fraction of *H. perforatum* on cellular and humoral immunity. Hyperforin is also a potent immunomodulatory agent by activating primary hepatocytes and IL-8 expression. Hyperforin is also responsible for inducing the encoding of intercellular adhesion molecule (inflammatory promoter) and expression of

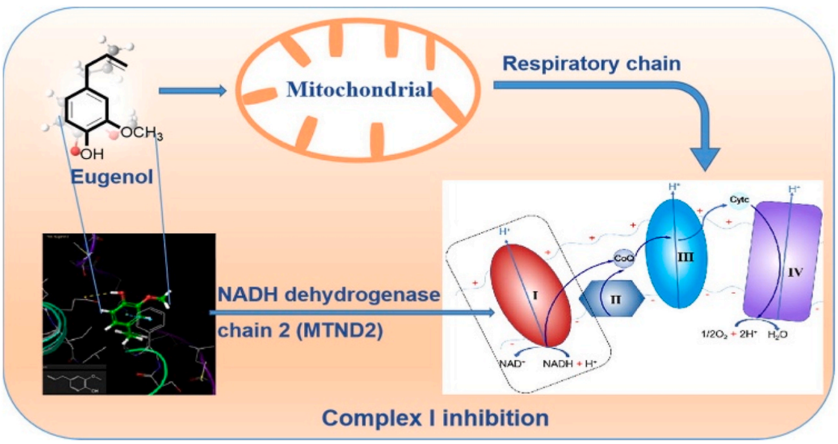

Fig. 11. Eugenol showed antioxidative activity [83].

mRNA [80].

5.6.6.5. Eugenol from Ocimumtenuiflorum (Labiatae). Eugenol is obtained from *Ocimumtenuiflorum* (syn. *O. sanctum*) and is reported to have significant adaptogenic/anti-stress properties. It is usually known as 'Tulsi' and its various parts have been extensively used in Ayurveda for the treatment of numerous disorders. *O. sanctum* (alcoholic extract) is claimed to possess immunomodulatory activity in animals. Hydroalcoholic extract of leaves of *O. sanctum* creates radioprotective activity in mice [81]. In a research study, eugenol reduced the TNF-α and IL-6 levels in cadmium toxicity induced liver inflammation by blocking inflammatory and signaling pathways which are involved in DNA damage and also by alleviating oxidative stress as shown in Fig. 11 [82].

5.7. Glycosides

5.7.1. Dihydrocoumarin from Aloe vera (Asphodelaceae)

Aloe vera is a popular and widespread plant with many therapeutic properties. Along with burn and wound healing potential, it also has significant immunomodulatory action. Dihydrocoumarin derivatives of this Anthraquinone glycoside show immunomodulatory activity by enhancing phagocytic function and by enhancing the formation of superoxide anions [84].

5.7.2. Mangiferin from Mangifera indica (Anacardiaceae)

M. indica is a most popular traditional medicinal plant which has been in use for a long time to cure many disorders such as anemia, low bp, rheumatism gingivitis, diarrhea, dysentery, etc. Animal studies showed that *Mangifera indica* possesses immunostimulatory activity. Mangiferin, an important compound of *Mangifera indica* possesses immunomodulatory activity through the enhancement of production of IgG1 and IgG2b [85].

5.7.3. Triterpenoid glycosides from Mollugoverticillata (Molluginaceae)

*M. verticillata*is a weed plant found in the American continent (warm and wet areas). The extract of *M. verticillata* showed immunomodulatory activity by directly enhancing the release of nitric oxide by peritoneal cells, but when these peritoneal cells are treated with the strains of Mycobacterium tuberculosis and BCG antigen then the response of the immune system is suppressed. Further studies have shown that quercetin and triterpenoid glycosides are responsible for immunomodulatory activity [86].

5.7.4. Irridoid glycosides from Plantago species (P. major & P. Asiatica) (Plantaginaceae)

P. major and *P. asiatica* which are species of Plantago have been in use over the years in the treatment of many immunopathogenic disorders. Iridoids glycosides of this medicinal plant are responsible for the modulation of the immune response through the transformation of lymphocytes and the release of IFN-γ [87].

5.8. Quinone

5.8.1. Thymoquinone from Nigella sativa (Ranunculaceae)

Thymoquinone is the primary active compound of the seed oil of *Nigella sativa*. It has been reported that seed oil affects immunomodulation through a decrease in the number of splenocytes and neutrophils. Instead of this, it increases the number of peripheral lymphocytes and monocytes. Thymoquinone showed immunomodulatory activity by T cell- and natural killer cell-mediated immune responses [88].

5.9. Proteins

5.9.1. Momorcharin from Momordica charantia (Cucurbitaceae)

M. charantia (bitter melon) is a well-known medicinal plant used traditionally for many disorders. Different parameters like IFN-γ, IL-4 were evaluated to detect the immunomodulatory activity. Momorcharin (α and β two abortifacient proteins) have been extracted from the seeds of this plant and a study on these showed that they are potent inhibitors of mitogenic responses of splenocytes of the mouse. Momorcharincan reduces macrophages' functions and delayed-type hypersensitivity response [89].

5.9.2. CM-Ala from Chelidonium majus (Papaveraceae)

Chelidonium majus (also known as swallow-wort) is a traditional medicine used for the treatment of liver disorders, skin infections, gastric ulcers, etc. In homeopathy and Chinese traditional medicine (CHM), *C. majus* has many medicinal applications such as it is used to treat jaundice, blood circulation blockage, and pain killer in edema [90]. CM-Ala, a protein (bounded with polysaccharide) is obtained from the water extract of *C. majus* in an investigational study for the immunomodulatory potential, it showed enhancement of granulocyte-macrophage colony-forming cells count as well as mitogenic activity on bone marrow cells and spleen. It also showed immunosuppressive action by reducing the count of epidermal Langerhans cells [91].

5.10. Steroidal saponins and sapogenins

5.10.1. Asparagus racemosus (Liliaceae)

Shatavari, a common name used for the *Asparagus racemosus* (mentioned as a Rasayana in Ayurveda) and has many medicinal properties such as it treats dyspepsia, gastric ulcers like problems. It consists of steroidal saponins and sapogenins (present in many parts of plants) which are responsible for the immunomodulatory activity. The immunomodulating property of Shatavari was evaluated using models (rat and mice) by protecting them against abdominal sepsis. Results showed that Shatavari (powdered root decoction) causes macrophages/polymorphs functions (phagocytic) improvement, leucocytosis with predominant neutrophilia. The percentage of mortality of animals (treated with Shatavari) was considerably decreased. Anti-sepsis activity by modifying the macrophage function demonstrates its significant immunomodulatory properties [92].

5.11. Polysaccharides

5.11.1. Glycyrrhizin and β-glycyrrhetinic acid from Glycyrrhiza glabra (Leguminosae)

The *Glycyrrhiza glabra* root extracts are used as a remedy for different ailments including both anti-inflammatory and anti-allergic diseases. Polysaccharides present in the hairy root and shoot of this plant are investigated and findings showed that polysaccharides have the potential to enhance the level of nitric oxide. The main constituents of *G. glabra* are glycyrrhizin and β-glycyrrhetinic acid which is considered to have immunomodulatory activity as β-glycyrrhetinic acid inhibits the classical complement pathway [93].

5.11.2. Alpha-tocopherol from Calendula officinalis (Asteraceae)

alpha-tocopherol, an active compound of *C.officinalis* showed strong immunomodulatory activity. A laser-activated *C.officinalis* extract (novel extract of *C.officinalis*)shows a strong inhibitory result on the development of *tumor* cells [94]. Along with these activities, it also has anti-genotoxic, anti-viral, and anti-inflammatory properties with skin infection treating ability [95].

5.11.3. CAVAP-I and CAVAP-II from Citrusaurantifolium (Rutaceae)

CAVAP-I and CAVAP-II are the two polysaccharides derived from *Citrus aurantium*. They differ from each other concerning the structure and molecular weight but they contain the same components in different amounts. The main components of these polysaccharides are arabinose, glucose, mannose, and galactose. In a study, it was found that CAVAP-II has greater immunostimulatory potential as compared to CAVAP-I. CAVAP-II activates c-Jun N-terminal kinase, phosphorylated extracellular signal-regulated kinase, P38, and P65 which results stimulate the formation of interleukin-6 and *tumor* necrosis factor-α, and inducible nitric oxide synthase [96].

5.11.4. Matricaria chamomilla (Asteraceae)

Heteropolysaccharides present in *M. chamomilla* have immune response stimulating effects. It causes normalization of an enhanced immune response (occurs due to air cooling except immersion cooling). Heteropolysaccharides stimulate the immune response by activating the immune response of erythrocytes, peripheral blood cells, and enhancing the responsiveness of effector cells towards helper signals [97].

5.11.5. Noni-ppt from Morindacitrifolia (Rubiaceae)

Noni-ppt is a polysaccharide-rich compound found in *Morindacitrifolia* (Noni) and is responsible for the immunomodulatory activity. *M. citrifolia* has been used as a traditional medicine for the treatment of a number of infections and disorders such as bacterial, fungal, and viral infections along with anti*tumor*, anti-inflammatory, hypotensive analgesic, and immunotherapeutic activities. Noni-ppt (collected from the alcoholic extract of *M. citrifolia*) activates the immune response of the host and this inhibits the growth of *tumor*s. Besides, it also prevents *tumor* necrosis factor-alpha, (TNF-α) production [98].

5.11.6. Tamarindus indica (Leguminosae)

T. indica (commonly called tamarind) is native to Asian countries and its fruit pulp is widely used as a spice, food component, juice, etc. Extract of fruit pulp of *T. indica* consists of polyphenols and polysaccharides. Because of the presence of polyphenols fruit pulp extract exhibited antioxidant, anti-atherosclerotic, and immunomodulatory activities. Instead of polyphenols, polysaccharides are also able to modulate the immune response. A polysaccharide from *T. indica* which mainly consists of glucose, mannose, and galactose modulates immune response through enhancement of phagocytic activity, inhibiting cell proliferation, and leukocyte movement [99].

5.11.7. Salvia officinalis (Lamiaceae)

Polysaccharides containing pectin, arabinogalactans, and glucuronoxylan-related polymers which are found in aerial parts of *S. officinalis* showed immunomodulatory effects through the enhancement of proliferation of thymocytes (studies using rat model) [100].

5.12. Organosulphur compound

5.12.1. Allium sativum (Alliaceae)

A. sativum is an important nutritional component and is popular around the world as garlic. A few pieces of evidence for modulating immune response by garlic or its components were found and acts by enhancing T-lymphocyte blastogenesis, phagocytosis, and altering cytokine production (both *in vitro* and *in vivo*). In a study, it was found in research that aged garlic extract exhibited anti-allergic and anti-tumor activity (Fig. 12) by preventing the growth of tumor cells and chemo-preventative effects [101]. The figure shows the preventive actions of garlic phytochemicals in different stages (initiation stage, promotion stage, and progression stage) of cancer progression. For instance, in the initiation stage, it blocks the activation of carcinogens by detoxication, anti-oxidation, and anti-mutagenesis mechanisms; whereas in the promotion and progression stage, suppressing phytochemicals causes anti-proliferation of clonal cells through DNA repair and protein folding modulation; and obstructs tumors growth by altering the cell behaviors, including apoptosis, anti-proliferation, and immunocompetence respectively [102].

6. Properties and possible mechanisms of phytoimmunomodulators

Immunomodulators are mitogens or anti-genomimetics i.e., instead of being real antigens, they only mimic their action. Its mode of action can be of two types: specific and non-specific. For the efficient functioning of anti-genomimetics, booster doses are necessary. The effectiveness of immunomodulators depends on factors like dosage administered, time and duration, and mode of drug administration [5]. A number of mechanisms (shown in Fig. 1) are involved to modulate immune response i.e., immunomodulatory action. Some primary mechanisms are stimulation of the phagocytosis process; enhancement of the activity of lymphoid cells; macrophages activation; immunostimulatory action on macrophages that resides in the peritoneal cavity; enhancement of antibodies (antigen-specific immunoglobulin) production; stimulation of specific and non-specific cellular immune responses; raise the number of natural killer cells, total white cells, interleukin-2 and mediators (non-specific); reduction of leukopenia (chemotherapy-induced) [2].

7. Current advancements and future possibilities

Immunomodulators can either be plant-derived or synthetic. Secondary metabolites-based immunomodulators (Phytoimmunomodulators) are herbal or natural and are less effective than synthetic immunomodulators. These are not as potent as synthetic immunomodulators and have been proved to cause less or no side effects as compared to synthetic medicaments [104]. The role of medicinal plants in the treatment of diseases and boosting the immune system has been under continuous experimentation for ages. There are different herbs with bioactive compounds and antiviral action which is having the possibilities as Immunomodulators that are shown in Table 2. This continuous experimentation and improved research technologies have led to the discovery of multiple herbal products and medicines which treat diseases and improve the immunity of human beings [105].

The challenges today in accepting the therapeutic effectiveness of herbal drugs are: There is no procedure for the standardization of products, no regulation for assuring the quality of pure chemical compounds, herbs, and herbal formulations. The WHO has also emphasized the need to use modern techniques to ensure the quality of herbs and their formulations. Another challenge is that the clinical trials are not done according to any documented standards, as there are none [106]. According to current studies, the fruit of the cucumber plant, *Cucumis melo* L, contains antioxidant, cytotoxic, antibacterial, anti-hyperlipidemic, diuretic, nephroprotective, anti-inflammatory, and anti-ulcer, properties. *Cucumis melo* contains a variety of biologically active substances that are essential to

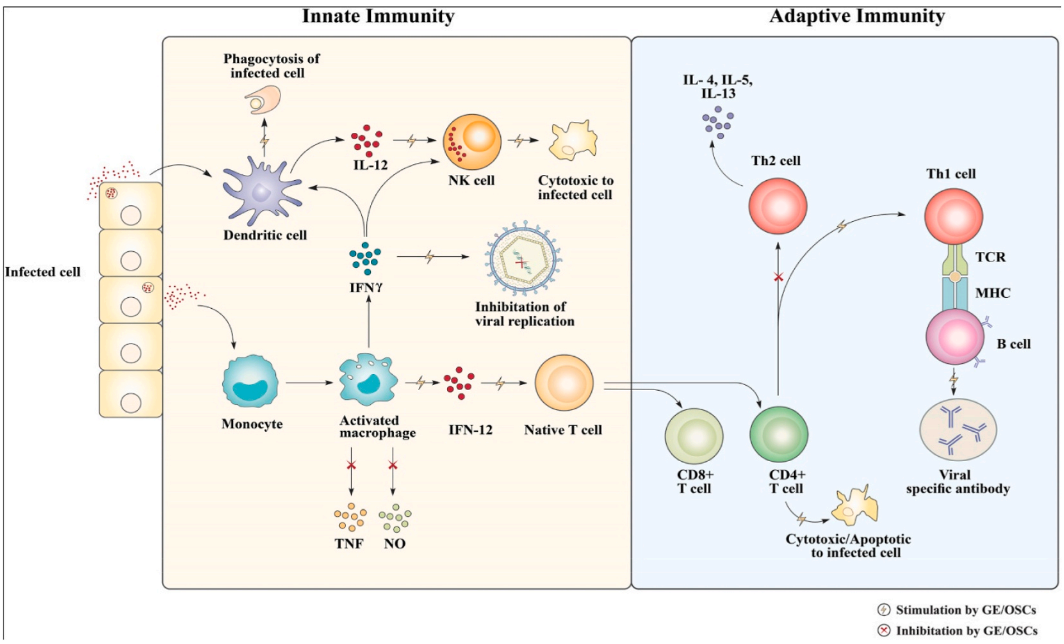

Fig. 12. A proposed molecular pathway of immunomodulatory effect of *Allium staivum* [103].

Table 2
Herbs with bioactive compounds and antiviral action with possibilities as Immunomodulators.

Herb	Bioactive compounds	Antiviral actions and recommended dose	Description
Giloy (Gilu) (*Tinospora cordifolia*)	It contains polysaccharides, phenolics, diterpenoids, steroids, and sesquiterpenoids.	*Tinospora cordifolia* in combination with conventional antiviral treatment shows significant effects on models (young chicks) against HIV and bursal diseases. A compound 1, 4-alpha-D-glucan extracted from *T. cordifolia* stimulates the immune system by activating macrophages, translocating NFκB, and enhancing the production of cytokines. Dose: 10–20 gm in the form of decoct.	Guduchi (in Ayurveda) and Gilu (in Unani) have immense medicinal uses such as blood purifiers, strengthening of the immune system, pain killer, antipyretic and anti-inflammatory properties. In Unani medicine, it is a preferred drug for the treatment of chronic cough, pneumatic, breathlessness, leprosy, and sexually transmitted diseases.
Saffron (Zafran) (*Crocus sativus*)	Safranal, crocin, and picrocrocin as well as it consists of about 150 volatile compounds.	It acts on humoral and cellular immunity and boosts the immune system. Dose: 1–2 g	It has cardioprotective, neuroprotective, nephron-protective, hepatoprotective, and anti-asthmatic activities.
Black cumin (Kalonji) (*Nigella sativa*)	thymoquinone, saponins, thymoquinone, carvacrol, *p*-cymene, alfa-pinene, as well as thymohydroquinone, sesquiterpene, a pentacyclic triterpene, and terpineol	It possesses potent antiviral activity against viruses like herpes simplex (type-1 virus), hepatitis C, H9N2, HIV, etc. Dose: 1–2 g	It also possessed immunomodulatory, analgesic, antioxidant, anticancer, antidiabetic potential along with protective effects against inflammation, asthma. It also acts as hepatoprotective, gastroprotective, and nephroprotective.
Indian gooseberry (Amla) (*Emblica Officinalis*)	gallic acid, ellagic acid, sesquiterpenoids, gearaniin, and prodelphinidins.	This is known to be effective against viral infections because of its extreme immune-enhancing ability. This is beneficial for the relief of common cold, bronchitis, pneumonia, AIDS, and cancer. Dose: 10 g	Amla is an effective antioxidant, anti-inflammatory, immune boosting, antipyretic, antitussive, hematinic, hepatoprotective, neuroprotective, and anticancer agent.
Turmeric (Chobzard) (*Curcuma longa*)	Curcumin, hexahydrocurcumin, dihydrocurcumin, and some volatile compounds i.e. cinol, α-phellandrene, borneol, zingiberine, and sesquiterpenes.	Curcumin was shown to be highly efficacious in the treatment of acute respiratory distress syndrome, COPD, acute lung infection, and pulmonary fibrosis. Turmeric acts as an effective anti-inflammatory agent by inhibiting TNF-α and NF-κB. Viruses such as H1N1, H6N1, respiratory syncytial virus, herpes simplex virus, parainfluenza virus type-3, coxsackievirus B3, Japanese encephalitis, hepatitis B and C virus, human papillomavirus-16, and -18 have been identified which are with extreme action of turmeric. It also suppresses repeat-directed gene expression of the long terminal HIV-1. Dose: 1–3g (powder or decoct from)	Unani therapeutic system states that it is often used as a phlegmagogue, analgesic, antipyretic, purifying blood, and other soothing properties. Scientists confirmed that it has antioxidants, immunomodulants, and other activities involving anti-inflammation, antimicrobials, and anticancer.
Licorice (Mulethi) (*Glycyrrhiza glabra*)	glycyrrhizin, glabridin, 18-beta-glycyrrhetinic acid, liquiritigenin, licochalcone A, and E.	Glycyrrhiza extract shows inhibitory action against viruses named hepatitis C, coxsackievirus B3 and A16, H5N1 influenza A, H3N2 influenza, human respiratory syncytial, and enterovirus 71; and also inhibits SARS replication. Dose: 3–7 gm (in the form of decoct)	It is also used to cure respiratory ailments, inflammatory reactions, and fever. It is used as a diuretic, immune-enhancer, and nerve stimulant. Current research findings have demonstrated that it is an effective anti-microbial, immunomodulator, anti-viral, and anti-tumor.
Hedge mustard (Khaksi) (*Sisymbriumofficinale*)	Its seed consists of isopropyl-isothiocyanate, butyl-isothiocyanate, phenylethyl alcohol, eugenol.	It indicates effective activity against leukotriene and histamine, antimutagenic activity, and protective actions against bacteria (gram-positive and gram-negative) which are resistant to ampicillin Dose: 5–7 gm (decoct form)	In the Unani medicine system, it is beneficial for curing all types of fever, measles, and chickenpox. It was also used in traditional medicinal systems for treating cough, cholera, and tuberculosis.
Neem (*Azadirachta indica*)	nimbin, nimbidin, nimbolide, limonoids, β-sistosterol, hyperoside and quercitin	Modulates the immune system. Dose: 6–10 gm (decoct form)	It has various properties like anti-oxidant, anti-cancer, anti-fungal, etc. it also works as a blood purifier.

plant bioactivities [107]. Investigations showed that laurel (*Laurus nobilis* L) has immunomodulatory capabilities that might make it a promising natural anti-inflammatory agent and enable the creation of novel anti-inflammatory medications [108].

Hence, there are a lot of future possibilities and suggestions that are considered worthy: The design of studies for clinical studies must be improved for the establishment of better herbal drugs. Corporations across the globe must contribute to pooling the research data to help in the research and development of new herbal formulations and improve the existing ones [13].

8. Strength and limitations of phytoimmunomodulators

Numerous health conditions have been successfully treated using immunomodulators. They excel at controlling the hyperactive immune response that is characteristic of autoimmune illnesses. Immunomodulators are useful for treating illnesses including rheumatoid arthritis, multiple sclerosis, and Crohn's disease because they reduce symptoms and enhance patients' quality of life [31,58]. Immunosuppressive medications, such as tacrolimus and cyclosporine, are essential in the field of organ transplantation because they prolong the lives of patients by preventing the rejection of transplanted organs. Additionally, by improving the immune system's capacity to identify and combat cancer cells, immunotherapies have transformed the way that cancer is treated and significantly increased the survival rates of several tumors. Immunomodulators have some noticeable risks despite their advantages. The greatest of them is the increased risk of infections brought on by immunosuppressive medications. These drugs weaken the immune system, making people more vulnerable to numerous pathogens and raising the risk of serious and potentially fatal illnesses. Additionally, immunomodulators commonly show adverse effects, which might include everything from weariness and skin concerns to gastrointestinal problems. From patient to patient, the kind and degree of side effects might differ, and they could need careful management. The effectiveness of these agents varies, which is another drawback. Different people may respond differently to immunomodulators, and some patients may have resistance or waning efficacy over time, necessitating the use of other therapies. Finally, and certainly not least, the variation in individual responses to immunomodulators might make treatment planning more difficult because what is helpful for one patient may not be the same for another. These restrictions emphasize the need for cautious planning and supervision while utilizing immunomodulators in clinical practice.

9. Future perspectives

A new age in healthcare is about to begin thanks to immunomodulators, a family of medications that can fine-tune the immune system. A study sheds insight on the immunomodulators' bright future prospects and shows how they have the ability to change how diseases are treated and prevented. The creation of more complex immunomodulatory drugs has recently been made possible by developments in immunology and biotechnology. These substances are adaptable weapons in the battle against a variety of illnesses since they may either stimulate or decrease immune responses. Immunomodulators' use in numerous medical fields will determine their future. Immunomodulators, which boost the body's capacity to identify and eliminate cancerous cells, are revolutionizing oncology cancer therapy. This has improved survival rates and minimized adverse effects. Additionally, immunomodulators show significant potential in the treatment of autoimmune disorders, where they can aid in reestablishing immunological balance and symptom relief. Additionally, the development of personalized medicine has made it possible to customize immunomodulatory medicines to the unique patient profiles, increasing efficacy and reducing side effects. Immunomodulators are at the forefront of efforts in infectious disease management to tackle new pathogens and overcome antibiotic resistance. These substances can improve the efficiency of vaccinations as well as the host's defenses against diseases. Additionally, immunomodulators are being researched more and more as preventative measures, with potential implications in disease prevention and immunization plans. It is important to recognize their contribution to tackling problems with global health, such as pandemics and epidemics. Immunomodulators' future also includes regenerative medicine, where they could make tissue healing and organ transplantation easier.

10. Conclusion

Several secondary metabolites of plants such as polyphenols, alkaloids, flavonoids, terpenoids, polysaccharides, etc. have the potential to induce changes in the immune response. Secondary metabolites are continuously being studied for their immunomodulatory properties to discover and develop herbal medicaments with fewer side effects, cost-effective, and highly effective properties. These studies are important for the effective treatment of disorders or diseases in which the immune system gets affected. It can be concluded that Phytoimmunomodulators proved to be significant regulators of immune reactions and also a beneficial herbal treatment for patients that need herbal medicaments to overcome the side effects of synthetic medicaments.

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CRediT authorship contribution statement

Partibha Hooda: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Rohit Malik:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Saurabh Bhatia:** Writing – original draft, Writing – review & editing. **Ahmed Al-Harrasi:** Data curation, Writing – original draft. **Asim Najmi:** Data curation, Writing – original draft, Writing – review & editing. **Khalid Zoghebi:** Data curation, Writing – original draft, Writing – review & editing. **Maryam A. Halawi:** Data curation, Writing – original draft, Writing – review & editing. **Hafiz A. Makeen:** Data curation, Writing – original draft, Writing – review & editing. **Syam Mohan:** Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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