Classification, Mode of Action and Uses of Various Immunomodulators

1

Prashant Kumar, Sweta Rai, Sunil Kumar Verma, P. Shakti Prakash, and Dheeraj Chitara

Abstract

Immunomodulators are substances found in nature that aid in immune system regulation. They are concoction operators that take part in insusceptible frameworks of the immune system. Commonly present immunomodulators were less significant compared to therapeutic immunomodulators. Immunomodulatory medicines, like 6-mercaptopurine and mycophenolate mofetil, conceal the safe framework and minimise irritation in the stomach tract in persons with inflammatory bowel disease and ulcerative colitis Crohn's disease. Their advantages come from their capacity to invigorate conventional and versatile safeguard systems, a kind of cytokines that empower the whole body. Immunosuppressants and immunostimulants are two categories of immunomodulators. Immunosuppressants are involved in smothering the invulnerable framework and handle neurotic safe reactions in the immune system like sickness and unite dismissal. Immunostimulants are agents that enhance the body's resistance in case of infections. It also improves the immune response, and people with the depletion of response are immunotherapeutic operators. For

P. Kumar (✉) · S. K. Verma
Department of Biotechnology, B. N. College of Engineering & Technology, Lucknow, Uttar Pradesh, India

S. Rai
Department of Pharmaceutical Chemistry, Kashi Institute of Pharmacy, Varanasi, Uttar Pradesh, India

P. S. Prakash
Department of Biomedical Engineering, School of Engineering and Technology, Mody University, Sikar, Rajasthan, India

D. Chitara
Department of Applied Sciences, Indian Institute of Information Technology, Allahabad, Uttar Pradesh, India

R. K. Kesharwani et al. (eds.), *Immunomodulators and Human Health*,
https://doi.org/10.1007/978-981-16-6379-6_1

example, various scatters, such as immunodeficiency state, immune system sickness, malignant growth, and viral contamination, can be treated with immunostimulants. In the subsequent decades of the twenty-first century, immunomodulators will become a viable assist in generating modalities that will provide a unique approach for treating irresistible diseases.

Keywords

Antigen · Antibodies · Transplantation · Immunomodulators · Immunosuppressant

1.1 Introduction

Immunology is characterised as natural defence mechanism against many diseases or disorders. The invulnerable framework is the body's most complex biological mechanism. The term insusceptibility characterises the natural defence system against the many diseases. The human immune system is very sophisticated and highly advanced among vertebrates; this immune framework is capable of generating boundless variety of cells and caught enormous spectrum of infections and foreign particles. The substances capable of inducing, amplifying or restraining any component or phase of the invulnerable framework are referred to as immunostimulators. Immunostimulators and immunosuppressants are two types of immunomodulators are known for use. Immunopharmacology is a more current branch of pharmacology concerned with immunomodulators (Patil et al. 2012). Administration of immunostimulators as in the case of AIDS and the utilisation of immunosuppressor in the cases of an exaggerated response of a safe framework are appreciating to reconstitute the normal resistant framework and increase the longevity of life. Immunomodulator intake, along with antigen, is meant to support the insusceptible framework. The modulator is the resistant framework's key role in distinguishing self from non-self. Immunisation can take place in two ways: actively or passively. In inactive immunisation, an antigen is stimulated to aid the body's development of immunological defences against potential exposure. Passive immunisation entails administering antibodies that have been preformed to the person who has already been exposed or is soon to be exposed to antigen. The activity of immunostimulant has been reported in several plants, and these plants utilised traditionally for rejuvenation of the immune system and treatment of chronic diseases in India, China and European countries. Currently, some stimulation of antigen-specific or non-specific invulnerability is evidenced by an increase in haemagglutinating antibody (Ha) titre and plaque-forming cells treated with half ethanolic extract of these plants in mice. The studies prove that these plant products play a vital role in rejuvenation therapy and chronic ailments of Indian traditional medicine (Patil et al. 2012). Around 122 chemicals inferred from plants have been

identified as therapeutic substances that are also used in commercial drugs. For example, the bark of the willow tree is rich in salicylic acid, which is also an active metabolite of aspirin, and this bark has been identified as a therapeutic substance (Goodman 1996). Some of the medications which are as often as possible utilised by the physicians are also determined from plant sources, for example, aspirin, digoxin, quinine, opium, etc. (Goodman 1996). They have been used as an herbal tranquilliser for a long time. There is a growing interest in using these medicinal plants as modulators of the complex safety system. Many chemical forms of alkaloids, flavonoids, terpenoids and polysaccharides have been discovered through many sorts of research conducted in the area (Puri et al. 2013); lactones and glycosides are the main factors for modification in the immunomodulatory properties.

1.2 Subtypes of Immunomodulators

Immunomodulators are divided into the three subtypes:

(a) Immuno-adjuvants improve vaccine efficacy and can be employed as particular immunostimulants. Immuno-adjuvants are the actual modulators of the fast response, acting as selectors between immune-protective and immune-destructive T1 (Th1) and T2 (Th2) cells (Dias et al. 2012).
(b) Immunostimulants are inalienably non-specific resistant to infection. These immunostimulants work in both innate and adaptive invulnerable responses. These immunostimulants serve as prophylactic and promoter compounds such as immunopotentiators—the immunostimulants with invulnerable response, which act as immunotherapeutic compounds (Wadood et al. 2013).
(c) Structurally and functionally, immunosuppressants are a diverse class of drugs frequently used in combination regimens to treat various autoimmune and allergy diseases (Billiau and Matthys 2001). Immunosuppressant decrease in resistance to infections may occur as a result of chemotherapeutic factors (Billiau and Matthys 2001).

Immunosuppressant clinical applications are as follows:

- To prevent transplanted organs and tissues from being rejected
- To treat graft-versus-host disease in bone marrow transplants
- To treat myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and ulcerative colitis, which are not entirely understood autoimmune components in their pathogenesis
- Avoiding Rh haemolytic disease in newborns with selective immunosuppression

1.2.1 Immunostimulant

The immunostimulation comprises a therapeutic concept which stimulates the non-specific immune system; this means that non-antigen-dependent stimulation is used to boost the efficacy of granulocytes, macrophages and natural killer cells.

Immunomodulator Drug Side Effects

Pulmonary toxicity, myelosuppression, alopecia and an increased risk of infection have been reported as side effects of these drugs (Kremer et al. 1994).

1.2.1.1 Pharmacognostic Approaches

Pharmacognostic approaches are briefly discussed in Table 1.1.

1.2.1.2 Chemistry of Phytoconstituents Used as Immunostimulants

1.2.1.2.1 Glycosides

These are organic compounds derived from plant and animal sources that, when hydrolysed by enzymes or acids, give one or more sugar moieties known as glycone parts. When water is lost, they create acetals and ether forms that connect with the hydroxyl groups of sugar and non-sugar moieties. Many glycosides are available for the ideal immunomodulatory action, such as:

- *Picrorhiza scrophulariiflora*, anthraquinone glycosides.
- Three novel sesquiterpene glycosides have been isolated from the stems of *Dendrobium nobile*: *Andrographis paniculata*, Dendroside and Dendronobilosides.

1.2.1.2.2 Flavonoids

Flavonoids are 15-carbon (6-3-6) skeletons with two phenyl rings that bind three-carbon.

Various forms of flavonoids, including apigenin, exhibit immunomodulatory activities.

- Oligomeric proanthocyanidins.
- Isoflavonoids, flavones and anthocyanins such as flavonoids are found in *Terminalia arjuna*.

1.2.1.2.3 Coumarins

Glycosides derived from benzo-a-pyrone are known as coumarins. Furanocoumarins are made by fusing furan ring to a coumarin at the 6 and 7 positions or the 7 and 8 positions (Leung et al. 2005), and these molecules show immunomodulatory activities. 6,7-Dihydroxycoumarin (esculetin) is a coumarin derivative extracted from a range of plants, including *Artemisia capillaris*, *Citrus limonia* and *Euphorbia lathyris*. It shows pleiotropic biological activities, such as inhibition of lipoxygenase, suppression of the oxidative reaction that damages DNA, inhibition of tyrosinase

Table. 1.1 Summary of immunomodulators produced from plants

Category	Botanical (family)	Ayurvedic name	Part used	Chemical constituents	Other biological activities
Sesquiterpenes	*Ocimum sanctum Linn. (Labiatae)*	Tulsi	Whole plant	Eugenol, carvacrol, derivatives of ursolic acid, apigenin, anthocyanins, flavonoids	Carminative, stomachic, antispasmodic, antiasthmatic, hepatoprotective (Nadkami 2005; Khare 2008; Singh et al. 2007; Vaghasiya et al. 2010)
Flavonoid	*Morus alba Linn. (Moraceae)*	Brahmdaru	Leaves, Bark, Fruits	Flavonoids, anthocyanins	Expectorant, hypocholesterolaemic, diuretic (Bharani et al. 2010)
Glycoside	*Panax ginseng Wall. (Araliaceae)*	Ninjin	Fruits, Root	Saponins such as ginsenosides, panaxdiol, panaxtriole, oleanolic acid	Adaptogenic properties, antiarrhythmic (Khare 2008)
Flavonoid	*Achillea millefolium C. Koch (Compositae)*	Yarrow	Leaves	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	Anti-inflammatory, antispasmodic, antipyretic, diuretic (Sharififar et al. 2009)
Anthraquinone glycosides	*Aloe vera Tourn. Ex Linn. (Liliaceae)*	Kumari, Ghritkumari	Leaves	Anthraquinone glycosides	Purgative, Emollient anti-inflammatory (Cooper and Turcasso 1999; Khare 2008; Hamman 2008; Sikarwar et al. 2010)
Diterpene	*Andrographis paniculata Nees (Acanthaceae)*	Kaalmegha	Leaves	Diterpenes	Hepatoprotective, antispasmodic, blood purifier, febrifuge (Khare 2008; Varma et al. 2011)
Saponin glycoside	*Asparagus racemosus wild. (Liliaceae)*	Shatavari	Roots	Saponins, sitosterols	Ulcer healing agent, nervine tonic, anti-gout (Nadkami 2005; Bopana and Saxena 2007)
Terpenoid	*Murraya koenigii (L) Spreng. (Rutaceae)*	Surabhini-Nimba	Leaves	Coumarin, Carbazole alkaloids, glycoside	Antifungal, insecticides (Khare 2008; Shah et al. 2008)

(continued)

Table. 1.1 (continued)

Category	Botanical (family)	Ayurvedic name	Part used	Chemical constituents	Other biological activities
Flavonoids	*Couroupita guianensis Aubl. (Lecythidaceae)*	Nagalinga	Fruits, Flower	Steroids, flavonoids, phenolics	Antifungal (Pradhan et al. 2009)
Alkaloid	*Tinospora cordifolia Miers (Menispermaceae)*	Amrita, Guduchi	Entire herb	Alkaloids such as berberine, tinosporic acid	Hypoglycaemic agent, antipyretic (Kirti et al. 2004; Nadkami 2005)
Flavonoid	*Lagenaria siceraria Mol. (Cucurbitaceae)*	Katu-tumbi	Leaves, fruit	Cucurbitacin, beta-glucosidase	Purgative, emetic (Deshpande et al. 2008)
Triterpenoid and flavonoid	*Terminalia arjuna Roxb. (Combretaceae)*	Arjuna	Leaves, Bark	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, hypertensive (Halder et al. 2009)
Flavonoid	*Bauhinia variegate Linn. (Caesalpiniaceae)*	Kanchana	Roots, Bark, Buds	Flavonoids, Beta-sitosterol, lupeol	Antifungal, astringent (Ghaisas et al. 2009)
Flavonoid	*Urena lobata Linn. (Malvaceae)*	Nagabala	Roots, Flower	Flavonoids	Diuretic, emollient, antispasmodic (Rinku et al. 2009)
Saponin glycoside	*Gymnema sylvestre R. Br. (Asclepiadaceae)*	Gurmar	Leaves	Sapogenins	Antidiabetic, diuretic, antibilious (Malik et al. 2009)
	Cordia superba Cham and C. rufescens A. DC. (Boraginaceae)	Shleshmaataka	Leaves, Fruit, Bark	Alpha-amyrin	Anti-inflammatory, antimicrobial (Costa et al. 2008)
Glycoside	*Picrorhiza scrophulariiflora Benth. (Scrophulariaceae)*	Kutki	Roots	Iridoid glycosides, amphicoside	Antioxidant (Smit 2000)
Flavonoid	*Heracleum persicum Desf. (Apiaceae)*	Golpar	Shrub	Flavonoids, furanocoumarins	Antimicrobial (Sharififar et al. 2009)
Alkaloids	*Cissampelos pareira Linn. (Menispermaceae)*	Paatha	Roots	Hayatine alkaloids	Antipyretic, analgesic, antilithic (Bafna and Mishra 2010)

Flavonoids	*Abutilon indicum Linn. (Malvaceae)*	Atibalaa	Whole plant	Flavonoids	Diuretic, antibacterial (Dashputre and Naikwade 2010)
Saponins	*Chlorophytum borivilianum Sant. F (Liliaceae)*	Safed musli	Roots	Saponins	Antifungal (Thakur et al. 2007)
Flavonoids	*Altherananthera tenella Coibola (Amaranthaceae)*	Snowball	Herb	Flavonoids, triterpenes	Antitumour, anti-inflammatory (de Agostino Biella et al. 2008)
Carbohydrate	*Cistanche deserticola (Orobanchaceae)*	Cistanche	Herb	Polysaccharide	Immunomodulator, mitogenic, comitogenic (Habijanic et al. 2001)
Coumarin	*Cliona celata (Clionaidae)*	Boring sponge	Sponge	Clionamide, dehydrocoumarin	Antibacterial (Kannan et al. 2007)
	Cordyceps militaris L. (Clavicipitaceae)	Militaris	Fungus	Cordycepin, cordyceps acid	Anti-inflammatory (Lu et al. 2007)
Alkaloids	*Crinum latifotium Andr. (Amaryllidaceae)*	Milk and wine lily	Herb	Alkaloids	Immunomodulator (Ismail and Asad 2009)
Terpenoids	*Dracocephalum kotschyi (Lamiaceae)*	Dragon'shead	Herb	Essential oil	Immunomodulator (Mikhaeil et al. 2003)
Carbohydrates	*Echinacea angustifolia (Asteraceae)*	Cone flower	Flowers	Polysaccharide	Treatment for common cold, immunomodulator (Gaur et al. 2009)
Glycoside	*Eclipta alba L. (Compositae)*	Bringraja	Leaves	Triterpenoid glycoside	Anticancer, antileprotic, analgesic, antioxidant, antimyotoxic (Jain et al. 2005)
Tennin	*Euphorbia hirta Linn. (Euphorbiaceae)*	Asthma weed	Herb	Quercitol, myricitrin, gallic acid	Anti-inflammatory, sedative, anxiolytic activity (Satpute et al. 2009)
Alkaloid	*Evolvulus alsinoides Linn. (Convolvulaceae)*	Shankhpushpi	Herb	Alkaloids	Brain tonic (Jafarian et al. 2010)

(continued)

Table. 1.1 (continued)

Category	Botanical (family)	Ayurvedic name	Part used	Chemical constituents	Other biological activities
Phenols	*Haussknechtia elymatica (Apioideae)*	Haussknechtia	Herb	Phenolics	Immunomodulator (Tanaka et al. 1999)
Carbohydrates	*Inonotus obliquus Pers. (Hymenochaetaceae)*	Chaga mushroom	Mushroom	Polysaccharide	Antitumour (Jeong et al. 2006)
Lignin	*Larrea divaricata DC. (Zygophyllaceae)*	Creosote bush	Herb	Lignans	Anti-inflammatory (Hung et al. 2007)
Carbohydrates	*Lycium barbarum Linn. (Solanaceae)*		Fruit	Polysaccharide-protein complexes	Antioxidant (Zheng et al. 2006)
Proteins	*Matricaria chamomilla (Rhabdoviridae)*	Chamomile	Flowers	Protein	Immunomodulator (Cherng et al. 2008)
Glycoside	*Mollugo verticillata L. (Molluginaceae)*	Carpetweed	Herb	Quercetin, triterpenoid glycosides	Immunomodulator (Kobayashi and De Mejía 2005)
Saponin	*Moringa oleifera L. (Moringaceae)*	Sahijan	Leaves	Vitamin A, B, C, carotenoids, saponins	Antioxidant (Wang et al. 2010)
Terpenoid	*Pestalotiopsis leucothes (Amphisphaeriaceae)*		Fungus	Terpenes	Immunomodulator (Noori et al. 2004)
Alkaloid	*Piper longum L. (Piperaceae)*	Pipali	Fruits	Alkaloids	Antioxidants (Steinbach and Stevens 2003)
Phenol	*Rhodiola imbricate Gray. (Crassulaceae)*	Roseroot	Rhizomes	Phenolics	Immunostimulating properties (Ballarin 2008)
Flavonoids	*Silybum marianum L. (Asteraceae)*	Milk thistle	Flowers	Flavonoids	Antioxidant (Chang et al. 2007)
Carbohydrate	*Salicornia herbaceae (Chenopodiaceae)*	Glasswort	Herb	Polysaccharides	Immunomodulator (Mungantiwar et al. 1999)
Carbohydrate	*Viscum album L. (Loranthaceae)*	Mistletoe	Leaves, young twigs, berries	Viscotoxins, polyphenols, polysaccharides	Antitumoural (Sredni et al. 1990)

Carbohydrate	*Thuja accidentalis (Arborvitae)*	White cedar	Leaves	Polysaccharides	Immunomodulator (Bonacorsi et al. 2009)
Flavonoids	*Ganoderma lucidum (Fr.) P. karst. (Polyporaceae)*	Reishi mushroom	Whole plants	Flavonoids, triterpenes	Antioxidant (Chang et al. 2007)
	Nyctanthes arbor-tristis L. (Oleaceae)	Paarijaata	Leaf, Seeds	Iridoid glucosides	Anti-inflammatory, antispasmodic (Jiménez-Medina et al. 2006)
Alkaloid	*Actinidia macrosperma C. F. Liang (Actinidiaceae)*	Actinidia	Fruits	Alkaloids, saponins	Antileprotic (Bhatt et al. 2010)
Carbohydrate	*Acacia catechu Wild. (Leguminosae)*	Khadira	Leaf	Flavonoids, quercetin	Hypoglycaemic, astringent (Killestein et al. 2003)
Carbohydrate	*Boswellia spp. (Burseraceae)*	Shallaki	Gum resin	Triterpenes, Ursanes	Hypoglycaemic (Ordway et al. 2003)
Terpenoid	*Hibiscus rosa sinensis Linn. (Malvaceae)*	Japaa	Flowers	Cyclopropanoids	Antidiarrhoeal, anti-inflammatory (Mali and Hatapakki 2008)
	Cleome gynandra Linn. (Capperdiceae)	Tilaparni	Leaf, seeds	Hexacosanol, kaempferol	Anti-inflammatory (Ebringerova et al. 2002)
Terpenoids	*Hyptis suaveolens (L) Poit. (Lamaceae)*	Tumbaaka	Leaf, Flowers	Lupeol, Beta-sitosterol	Carminative, antispasmodic (Sugumaran and Robinson 2010)
Saponin	*Randia dumetorum Lamk. (Rubiaceae)*	Madana	Fruits	Saponins, triterpenes	Chlorosis, antiarthritic (Hsu et al. 2008)
Flavonoids	*Allium hirtifolium Boiss. (Alliaceae)*	Persian shallot	Herb	Thiosulphinates, flavonoids	Antirheumatic, anti-inflammatory (Zvetkova et al. 2001)
Flavonoids	*Citrus natsudaidai Hayata (Rutaceae)*	Japanese summer grapefruit	Fruits	Auraptene, flavonoids	Antioxidant (Amirghofran et al. 2000)
Carbohydrate	*Acanthopanax sessiliflorus (Rupr. & Maxim.) (Araliaceae)*	Prickly spine	Shoots, roots	Biopolymers	Lympho-proliferative activity (Senchina et al. 2005)

(continued)

Table. 1.1 (continued)

Category	Botanical (family)	Ayurvedic name	Part used	Chemical constituents	Other biological activities
Lipid	*Agelas mauritianus (Porifera)*	Agelas	Sponge	Glycolipid	Phagocytic activity (Jayathirtha and Mishra 2004)
Carbohydrate	*Aphanothece halophytica (Chroococcales)*		Cyanobacterium	Exopolysaccharide	Inhibits influenza virus (Patel et al. 2009)
Flavonoids	*Apium graveolens Linn. (Apiaceae)*	Celery seeds	Leaves, Seeds	Flavonoids, coumarins	Anti-inflammatory (Ganju et al. 2003)
Protein	Genus *Ardisia (Myrsinaceae)*	Marlberry	Shrub, Branches	Peptides, saponins, isocoumarins	Antimetastatic drug, anti-HIV property (Amir et al. 2007)
Tennin	Genus *Aristolochia (Aristolochiaceae)*	Pipevine	Leaves	Aristolochic acid	Antiangiogenic, employed in prostate cancer (Chen 2007)
Alkaloid	*Artemisia annua Linn. (Compositea)*	Wormwood	Herb	Artemisinin	Immunosupressive (Davicino et al. 2007)
Hydrocarbon	*Genus aspergillus (Trichonomaceae)*	Aspergillus	Fungus	Polyene, triazole	Antifungals (Gan et al. 2003)
Lipid	*Botryllus schlosseri*	Botryllus	Tunicates	Cytokines	Antioxidant, antiviral, antimicrobial, antitumoural (De Souza Reis et al. 2008)
	Bidens pilosa L. (Asteraceae)	Beggar-ticks	Flowers, Leaves	Polyacetylenes	Anti-inflammatory, immunosuppressive, Antimalarial, antibacterial (Ferreira et al. 2003)
Alkaloids	*Boerhaavia diffusa (Nyctaginaceae)*	Punarnava	Herb	Alkaloids	Immunostimulatory (Gupta et al. 2010)
	Bugula neritina L. (Bugulidae)	Brown bryozoans	Marine invertebrates	Macrocyclic lactones	Immunomodulator (Kumar et al. 2005)
Flavonoids	*Byrsonima crassa Nied. (Malpighiaceae)*	Byrsonima	Leaves	Flavonoids, terpenes, tannins	Antimicrobial, antioxidant (Sunila and Kuttan 2004)

Carbohydrates	*Calendula officinalis L. (Asteraceae)*	Garden marigold	Flowers	Polysaccharides, proteins, fatty acids, flavonoids, carotenoids, triterpenoids	Antitumour, antiviral, anti-HIV propertis (Mishra et al. 2008)
Tennin	*Camellia sinensis L. (Theaceae)*	Tea	Leaves	Epigallocatechin gallate, quercetin, gallic acid	Anticancer, Lipid lowering, Anticataract activity, Hepatoprotective, antioxidant (Meeran et al. 2006)
Alkaloid	*Cannabis sativa (Cannabaceae)*	Common hemp	Leaves	Cannabinoids	Immunomodulator (Im et al. 2006)
Alkaloid	*Carpobrotus edulis L. (Aizoaceae)*	Fig marigold	Flowers, fruit	Alkaloids	Immunomodulator (Elluru et al. 2007)
Glycoside	*Centella asiatica Linn. (Umbelliferae)*	Brahmi	Herb	Triterpenoid saponins	Immunomodulator (Gohla et al. 1992)

activity and antitumour activities (Thanh et al. 2004). The root of *Angelica dahurica* is used to assess cytotoxic coumarins (Jafarian et al. 2010).

1.2.1.2.4 Sapogenins

Sapogenins such as triterpenoid saponins and diterpenes modulate a broad spectrum of immunomodulatory activities. Some examples are *Gymnema sylvestre*, *Chlorophytum borivilianum*, *Boswellia* spp. and *Randia dumetorum*.

1.2.1.2.5 Alkaloids

These essential compounds, found in natural and synthetic forms, contain one or more nitrogen atoms. These alkaloids are found in heterocyclic form and have particular physiological effects on humans or animals. Some well-known alkaloids are *Achillea millefolium*, *Murraya koenigii*, *Cissampelos pareira* and *Actinidia macrosperma*.

1.2.1.2.6 Thiosulphinates

These compounds, such as *Allium hirtifolium*, have potent immunomodulatory as well as adaptogenic effects (Alamgir and Uddin 2010).

1.2.1.2.7 Volatile Oils and Terpenoids

Terpene is a hydrocarbon (C5H8) chain, while terpenoids are hydrocarbons with oxygenated derivatives. Terpenes and terpenoids are plant and animal origin volatile oils. Many plants show immunomodulatory activity with terpene moiety display, e.g. eugenol derived from *Ocimum sanctum*.

1.2.1.2.8 Polysaccharides

The regulation of innate susceptibility and, more particularly, the macrophage characteristic of polysaccharides has several therapeutic advantages. Both microbial and botanical polysaccharides bind to the surface receptors in macrophages that induce immunomodulatory responses. Both forms of organisms share these evolutionarily conserved polysaccharide structural features. The evaluation of botanical polysaccharides reveals beneficial immunomodulatory properties, providing a rare opportunity to discover novel therapeutic compounds—polysaccharides activate monocytic cells and induce monocytic cell differentiation into macrophages (Allison 2000; Ríos 2010).

1.2.2 Immunostimulant Synthetic Drugs

Immunostimulants are attractive substances that activate the invulnerable framework of animals to improve the natural resistance to many bacterial and viral infections. These biologically active substances are derived from natural sources or synthesised using various chemical properties and action mechanisms. In general, immunostimulants induce the amalgamation of specific antibodies and cytokines for the treatment of infectious diseases. These immunostimulants are divided into

two groups: first, specific immunostimulants that function as antigens for the stimulation of immune responses (e.g. vaccines) and, second, non-specific immunostimulants that have no antigenic properties yet enhance healthy responses to other antigens (e.g. adjuvants and non-specific immunostimulants).

The origin and mode of action of these immunostimulants are classified (Labh and Shakya 2014).

1.2.2.1 Functions of Immunostimulants

Immunostimulants activate various components of the insusceptible framework in animals and humans. They develop the non-specific immunotherapy and immunoprevention by stimulating the significant factors of the resistant framework including phagocytosis, properdin and complement frameworks protective secretory Iga antibodies, α- and γ-interferon release, T- and B-lymphocytes, combination of specific antibodies and cytokines, and blend of pulmonary surfactant (Petrunov et al. 2007). There are several reasons to use immunostimulants to treat various infectious diseases, including bacteria's antibiotic resistance, allergic reactions to antibiotics, immunosuppressive effects of antibiotics and poor effects of antibiotics in viral infections (Petrunov et al. 2007).

1.2.2.2 Types of Immunostimulants

Immunostimulants were divided into seven groups for better understanding: bacterial products, complex carbohydrates, vaccines (antigens and adjuvants), cytokines, immunoenhancing products, plant extracts and animal extracts. Few immunostimulatory drugs (endogenous immunostimulants or synthetic immunostimulants) have been developed to induce humoral or cellular fast responses against bacterial or viral infections, immune deficiency diseases and cancer. They were classified as follows:

1.2.2.2.1 Levamisole (Ergamisol)

Levamisole is a synthetic immunostimulant that stimulates B- and T-lymphocytes, as well as monocytes and macrophages. It was used in adjuvant therapy with 5-fluorouracil after surgical resection in patients with colon cancer. Allergy, nausea, influenza and muscle pain are some of the common disadvantages. Levamisole has been successfully used in combination with polymers to treat dermatological disorders. For example, it was combined with cimetidine to treat recalcitrant warts and with prednisolone to treat aphthous ulcers of the mouth (Patil et al. 2012; Biswajit et al. 2014).

1.2.2.2.2 Thalidomide

Thalidomide or immunoprin (C13H10N2O1) is an immunomodulatory drug. In patients with erythema nodosum leprosum, thalidomide can reduce circulating TNF-α. In HIV-positive patients, however, it increased TNF-α. Furthermore, it was able to overcome its therapeutic effects in severe rheumatoid arthritis and angiogenesis. Isoprinosine (Inosiplex/Imunovir): Isoprinosine (C52H78N10O17) is a combination of inosine, acetamidobenzoic acid and dimethylaminoisopropanol.

Isoprinosine could enhance the levels of cytokines, including IL-1, IL-2 and IFN-γ. In response to mitogenic or antigenic stimuli, it boosted lymphocyte proliferation. Isoprinosine also augmented active T-cells and induced T-cell surface markers on prothymocytes. It was utilised to treat Herpes simplex infections, Epstein-Barr and measles infections. Its disadvantages include a milder CNS depressant, temporary nausea and higher serum and urine uric acid levels (Patil et al. 2012).

1.2.2.3 Immunocynin

Immunocynin is a stable form of hemocyanin, a copper-containing protein, which is found in molluses and arthropods. It was utilised to treat urinary bladder cancer with reduced side effects, such as rare yellow fever (Patil et al. 2012).

1.2.2.3.1 Bestatin

Bestatin, a dipeptide [(2S, 3R)-3-amino-2-hydroxy-1-phenylbutanoyl]-L-leucine, is a low-toxicity immunostimulant that binds to lymphocytes and macrophages and enhances both humoral and cellular safe responses. It is an inhibitor of leucine aminopeptidase and aminopeptidase-B—bestatin possesses antitumour activity and also increases the antitumour activity of bleomycin and adriamycin. Bestatin was effective in preventing the metastasis of P388 leukaemia when the antibiotic was regularly injected after tumour inoculation (Tsuruo et al. 1981); the dipeptide was immunorestorator in the elderly and cancer patients and HIV-infected subjects. In vitro enhanced granulocytopoiesis and thrombocytopoiesis, which might restore them in myelohypoplastic men (Mathe 1991).

1.2.2.3.2 Bacterial Products

The effect of immunostimulatory are due to the release of cytokines from bacteria. Its immunostimulatory mechanism is caused by bacteria that (a) induce a granulomatous reaction at the site of administration and (b) prevent and treat carcinoma forms. This mechanism causes phagocytosis and resistance to infection through B- and T-cell-mediated responses. Some disadvantages are excessive touchiness, fever, shock and complex insusceptible disease (Patil et al. 2012).

1.2.2.3.3 Recombinant Cytokines

Many interferons and interleukins stimulate immune reactions. After stimulation with mitogens, interferons could be obtained from trout leucocytes. It could cause in vitro resistance to pancreatic necrosis infection in trout cells. Low doses of interferon could induce stable positive outcomes in mammals without causing side effects. On the other side, vaccination of animals with the recombinant IL-2 increased the protective effects against specific infections. In large dosages, IL-2, on the other hand, was a highly hazardous compound, causing symptoms, such as fever and diarrhoea. The cleaned cytokines produced unsatisfactory results in clinical trials because the resistant responses were produced by a blend of cytokines generated by the safe cells rather than against a single cytokine. In this way, non-specific cytokine amalgamation enhancers will develop safe responses and solve the problem (Galeotti 1998). Thus, recombinant cytokines are produced

recently in various expression frameworks (e.g. plants) and utilised in clinical trials, such as interferons, TNF-α and IL-2 (Sirko et al. 2011).

1.2.2.4 Complex Carbohydrates

Several types of complex carbohydrates were described as follows:

1.2.2.4.1 Glucans

The β-(1→3)-linked chain of glucose units is an essential class of immunostimulants.

There are β-(1→6)-branched glucose units in the main chain. The β-glucans were derived from unusually well-preserved structural components of cell walls in organisms, algae and yeast and have a wide range of molecular weights ranging from 5 to 200 kDa. Depending on the source, the length and frequency of these branches vary. B-glucan has been used to stimulate antitumour mechanisms (e.g. increased macrophage activity) and to improve host resistance to a variety of microbial pathogens in mammals. Glucan may also be beneficial in preventing aflatoxin's carcinogenic effects. The β-glucan was thought to be a stimulator of cell invulnerability. In fact, in the presence of glucans, mammalian macrophages or monocytes have specific receptors for glucans and their precursors, such as cytokines (e.g. IL-1, IL-9, TNF-α) and prostaglandins (Sahoo and Mukherjee 2001; Madrigal-Bujaidar et al. 2015). In Japan, β-glucans such as lentinan, derived from shiitake mushroom, and Polysaccharide-K, derived from *Coriolus versicolor*, were licensed as anticancer drugs. Lentinan may induce protective Th1 insusceptible responses to control the proliferation of malaria parasites in red blood cells by stimulating the maturation of Dcs; increasing the expression of MHCII, CD80/CD86 and Toll-like receptors (TLR2/TLR1) and the level of IL-12; and forestalling the adverse effects of Tregs. The primary roles of glucans have been discovered in the treatment of cancer, infection resistance, stress reduction and the restoration of damaged bone marrow. Zymosan, a combination of polysaccharides isolated from the cell walls of *Saccharomyces cerevisiae*, could potently stimulate macrophages and induce neutrophil cytokine release. In reality, β-glucan in zymosan was recognised as its active component for non-specific immunomodulation. Also, β-glucan may also be able to reverse myelosuppression generated by chemotherapeutic medicines by targeting the C3 fragment of complement and circulating antibodies. Recent studies have shown that daily therapy with soluble or insoluble β-glucan reduced tumour size by 70–95%. To be sure, after the coupling of antibodies on the surface of cancer cells, C3 fragments of complement could coat the cancer cells at that point, β-glucan-prepared cells, such as neutrophils, macrophages and NK cells, correctly recognised these complement-antibody complexes and executed the tumour cells. The cooperation of β-glucan with antitumour antibodies is a practical approach in combination treatment (Vetvicka 2011).

1.2.2.4.2 Trehalose

Trehalose dimycolate (TDM), muramyl dipeptide (MDP) and lipopolysaccharides (LPS) as bacterial products promote the production of antibodies, stimulate lymphocyte activation and elicit specific susceptibility to bacterial infections. Trehalose dimycolate, a glycolipid found in *Mycobacterium*'s cell wall, is a potent immunostimulant that inhibits tumour growth and improves resistance to bacterial, parasitic and viral infections. Because of their amphipathic properties, they can interact with membranes. TDM primes murine macrophages to produce nitric oxide (NO) and develop the antitumour activity. TDM, as an adjuvant, enhances both cellular and humoral invulnerability while eliciting a more robust cellular response. TDM could induce potent safe responses against malaria antigens in comparison to groups infected with malarial antigens and Freund's adjuvant. The results showed that in macrophage-drained mice injected with silica particles, the protective effect of TDM is reduced, indicating the role of macrophages.

T-lymphocytes were not required for TDM to activate peritoneal macrophages. Trehalose diesters could activate IL-12p10 and IFN-γ mRNA (Parant et al. 1978; Oswald et al. 1997).

1.2.2.4.3 Prebiotics

Prebiotics are inedible filaments that increase beneficial gut commensal bacteria, improving the health of the host. Prebiotics, such as fructooligosaccharide, mannan oligosaccharide, inulin or β-glucan, are known as monosaccharides. They significantly boost innate insusceptible reactions, such as phagocytic activation, neutrophil activation, alternative complement framework activation and increased lysozyme activity. Immunosaccharides interact with pattern recognition receptors (PRR) conveyed on innate invulnerable cells to directly activate the innate safe framework. In order to activate innate safe cells, they can also be linked to microbe-associated molecular patterns (MMPs). Probiotics activate the innate safe framework in two ways: (a) by directly stimulating the innate invulnerable framework and (b) by boosting the growth of commensal microbiota (Song et al. 2014).

1.2.2.5 Immunostimulants Used in Vaccines

Vaccines include a vast variety of immunostimulants; for example, an adjuvant heat-labile enterotoxin from *Escherichia coli* (LT), administered in the form of immunostimulant (LT-IS) patch on the skin, may improve insusceptible responses to influenza vaccination in the elderly. The invulnerable activation induced by LT-IS enhanced the potency of generating Alzheimer's disease (AD)-specific vaccination reactions as an adjuvant in the clinical trial (Davtyan et al. 2014). Co-administration of a potent adjuvant in IS patches containing heat-labile enterotoxin from *E. coli*. The anti-influenza antibody insusceptible response was significantly increased when *E. coli* was applied to the skin at the location of DNA vaccination (Mkrtichyan et al. 2008); adjuvants enhance and modulate resistant responses to antigens. This is important when the sanitised antigens do not elicit effective innate or adaptive resistant frameworks. Adjuvants are diverse in the sorts and levels of invulnerable responses. Expected advantages of adjuvants contain more robust resistant

preparing, effective invulnerable responses in low-response populations (e.g. the older or immunocompromised patients), the utilisation of smaller amounts of the antigen and safety profile (Garcon et al. 2011). New adjuvants have already applied to more efficient influenza vaccines, as well as vaccines targeting hepatitis B (HBV) and human papillomavirus (HPV) (Frech et al. 2005). On the other hand, CpG oligonucleotides and imiquimod drugs (an antiviral compound) could activate dendritic cells, induce in situ maturation and migration of Dcs and augment both humoral and cellular insusceptible responses (Frech et al. 2005). The unmethylated CpG motif in bacterial DNA was recognised as a B-cell stimulating adjuvant, and synthetic oligodeoxynucleotides (ODNs) containing the CpG motifs were shown to induce potent therapeutic activities in various infections and tumour animal models. Imiquimod was topically utilised for patients with anogenital warts as well as basal-cell carcinoma. The investigations indicated that CpG ODNs and imiquimod (resiquimod) drugs act as synthetic ligands for TLR9 and TLR7, respectively, and both stimulate Dc maturation efficiently (Frech et al. 2005).

1.2.3 Immunosuppressant

1.2.3.1 Synthetic Drugs: Manufactured Medications

Medications to smother human response against resistant have been used for couples of the decade. Such compounds were used for patient treatment undergoing organ transplantation or suffering from autoimmune diseases. The major stumble back of primitive immunosuppressive compounds was due to absence of specificity. Wide suppression of safe cell replication and cell function sometimes leads to extreme toxicities and related adverse symptoms. As the knowledge of invulnerable framework response for molecular and cellular level evolved, more current with specific compounds were developed which target particular component with its safe response. These modern immunosuppressive compounds do not have potential adverse effects with their efficacy and safety had significantly risen above to there predecessor compounds (Allison and Eugui 2005).

1.2.3.2 Immunosuppression for Organ Transplantation

Medications that suppress the human resistive response are widely used to prevent the rejection of transplanted organs (alloimmunity) and to treat autoimmune disease (autoimmunity). Solid-organ transplantation mostly involve the heart, liver, kidney and lungs (Libby and Pober 2001). The main objectives of transplant immunosuppression are:

- To forestall rejection of transplanted organs
- To limit sedate toxicity along with side effect
- To limit hazard of infection

In an ideal condition, these three goals could be fulfilled utilising most minor medications and the minimum possible dosage that could be effective in patients

along with graft survival. Transplantational tissue rejection occurs in three phases: hyper-acute, acute and chronic. Hyper-acute rejection includes a spontaneous (in practically no time) response from the recipient's an resistant framework against transplanted tissue and, which is expected due to measures taken by antibodies counter to donor H.L.A (human leukocyte antigen or A.B.O antigen-6 Eradication of transplanted tissues could be quick and broad. Precise matching between donor and recipient tissues can forestall this rejection type. Acute rejection type is most likely to incur inside initially 1–3 months post-transplant. Acute rejection is caused primarily due to host T-cells. When triggered by foreign antigens on the donor tissue, cytotoxic T-cells enter the organ and begin disintegration by releasing cytotoxic catalysts and proteins (e.g. perforins). Treatments that decrease T-cell activity work effectively for this type of acute rejection. In acute rejection, humoral-mediated rejection is crucial because host B-cells sharpen to donor tissue by producing antibodies against it. Antibodies directed against endothelial cells of the heart tissue can cause vasculature damage in acute rejection. This method of treating acute rejection is not particularly well known.

1.2.4 Inhibitor of Lymphocyte Gene Expression

Immunosuppression is used in transplant patients for various reasons, including preventing acute rejection in the days following the transplant. In order to do this, induction therapy is started during the transplantation surgery and lasts typically for 7–10 days. The infusion of a robust immunosuppressive antibody that blocks T-cell activation is typically used in induction treatment. Daclizumab and basiliximab, two of these drugs, are antibodies to the T-cell D25 (D 5 cluster of differentiation) receptor. Interleukin-2 has a high affinity for activating this T-cell receptor (IL-2). Even though activated T-cells can only transmit D25, these agents are very selective for T-cells already activated by MH. Daclizumab is a "humanised" antibody with 90% human components and is expected to be less antigenic than basiliximab, which has 75% human components. For both induction and acute rejection therapy, two polyclonal anti-thymocyte globulins are available. The first antibody, tgam, is generated from horses, while rabbits determine the second (Thymoglobulin). Both are linked to lymphocyte D receptors in a variety of ways. Once bound, antithymocyte globulins promote complement-mediated lysis of T-cells, resulting in their depletion. Both compounds are robust immunosuppressants, and transplanted patients might be exposed to a variety of infections because of their broad mechanism. Restriction of the globulins can cascade a chain of release for cytokines from T-cells, leading to "cytokine release syndrome", which causes headaches, fever, cold and vomiting in patients. The murine-inferred monoclonal muromonab (OKT3) is the third type of immunosuppressive antibody. This globulin binds to the CD3 cell surface receptor on T-cells, crucial in T-cell activation. Patients may produce donor organ trustworthiness and function since OKT3 is a murine protein. Cellular and humoral processes appear to be involved. Chronic inflammation of the donor tissue is a central feature of chronic rejection. T-cells release

cytokines when they are activated, which attract and activate macrophages. The donor tissue is then infiltrated by macrophages, which attack it with cytolytic compounds. Continuous antibody production by activated B-cells and the resulting activation of complement proteins may lead to chronic rejection. The retransplanting approach is the only option because there is no effective pharmacologic therapy for avoiding chronic rejection.

1.2.5 Antibodies Against Specific Immune Cell Molecules

Antibodies are Y-shaped proteins produced by the immune system in response to infection. For example, they help remove disease-causing bacteria from the body by crushing them or preventing them from contaminating cells. Antibodies function profoundly by perceiving and adhering to particular proteins, such as those present on the surfaces of pathogens and microorganisms, when the body encounters an organism simply because insusceptible cells develop antibodies that directly perceive proteins relevant to that specific microorganism. In the wake of recouping from a disease or getting an immunisation, few of these counteracting agents creating resistant cells, for the most part, stay in the body as memory cells, furnishing insusceptibility to future contaminations with a similar bug. Since memory cells and antibodies are now present, the body experiences a similar organism; the invulnerable reaction is quicker and can prevent the disease from grabbing hold. Antibodies that perceive the body's proteins rather than proteins from irresistible organisms can cause hurt. In immune system ailments, such as lupus, numerous sclerosis and rheumatoid joint pain, individuals produce antibodies that adhere to their body's proteins and assault solid cells.

Hypersensitivities include an exceptional class of antibodies called immunoglobulin E (IgE). When these antibodies recognise allergens, they cause invulnerable cells to release histamine and other irritating particles, resulting in severe side effects from unfavourably susceptible responses. Antibodies are mostly used in biomedical research because of their unique ability to recognise and cling to specific proteins, such as determining whether a given protein is present in a sample or where a specific protein is located within a cell.

1.2.5.1 Polyclonal Antibodies Antithymocyte Globulin (ATG)

Antithymocyte globulin is a pure type of gamma-globulin derived from rabbit serum immunised against human thymocytes (Sharma and Sharma 2007).

1.2.5.1.1 Mechanism of Action

Antithymocyte globulins have cytotoxic antibodies that will bind to CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44 and CD45, as well as HLA class I and II in the surface of human T-lymphocyte cells. The antibody drains circulating lymphocyte by direct cytotoxicity of complement and cell-mediated, which in turn block lymphocyte function by binding to the cell surface molecule engaged in cell activity regulation (Katzung 2012).

1.2.5.1.2 Therapeutic Uses

One of the major uses is in severe renal transplantational rejection.

1.2.5.1.3 Adverse Effects

Rigors, hypotension, serum sickness, glomerulonephritis, leucopenia with thrombocytopenia and increased risk of infection with malignancy are some of the main effects when several immunosuppressive compounds are used together (Golan et al. 2011).

1.2.5.2 Monoclonal Antibodies: Muromunab (Anti-CD3 Antibodies, OKT3)

An antibody targeting CD3, a trimeric structural molecule adjacent to the T-cell receptor in the surface of human T-lymphocytes, has been used in human transplantation with remarkable success since the early 1980s (Sharma and Sharma 2007).

1.2.5.2.1 Mechanism of Action

Muromonab-CD3 binds to the CD3 chain, a monomorphic component of the T-cell receptor complex involved in antigen recognition, cell signalling and preference.

The use of antibodies induces a rapid internalisation of T-cell receptors, which prevents antigen recognition. The antibody is administered by depleting and extracting full T-cells from peripheral lymph organs (Carlos and Harlan 1994). The lack of traceable T-cells from individual lymphoid organs leads to secondary T-cell death, characterised by implementation activation, activation-induced T-cell passing and the marginalisation of T-cells in the vascular endothelial wall as well as redistribution of T-cells to the non-lymphoid organs. Muromonab-CD3 reduces T-cell function, as explained by a lack of interleukin-2 production coupled with massively reduced production of several cytokines, except interleukin-4 and interleukin-10 (Katzung 2012).

1.2.5.2.2 Therapeutic Uses

Cases of severe organ transplant rejection.

1.2.5.2.3 Adverse Effects

High fever, cold with headache, tremor, nausea, diarrhoea, abdominal pain, malaise, myalgias and arthralgias along with generalized weakness; minor effects such as skin allergy, cardiorespiratory issues and central nervous system disorders including aseptic meningitis; and potential fatal severe pulmonary oedema and acute respiratory distress syndrome (Tortora Gerard and Derrickson Bryan 2008).

1.2.6 Inhibitors of Immune Cell Adhesion

Cell-cell and cell-lattice attachments are known to assume critical jobs in the enlistment and enactment of insusceptible T-cells. Noticeable among the subatomic attachment parts are integrins (β1 and β2) that intercede the collaborations of an

assortment of insusceptible cells to extracellular frameworks and other resistant cells, separately (Adutler-Lieber et al. 2014).

Adhesion molecules can be classified into four major groups: integrins, selectins, cadherins and immunoglobulin superfamily (IgSF), including nectins and mucins (Samanta and Almo 2015). Along with the conventional adhesion molecules, the specific enzyme vascular adhesion protein 1 (VAP-1) plays an important role in cell adhesion (Jalkanen et al. 2007). Compounds that block leucocyte adhesion, transmigration with expression of related CAMs present therapeutic model as immunosuppressive and anti-inflammatory drugs (Hynes 1992).

For the most part, a cell adhesion inhibitor are classified as target site for cell-cell adhesion with expression of cell adhesion molecules (Jia et al. 2015), though certain small molecules such as flavonoids (Kobuchi et al. 1999) and others (Mun et al. 2011). When the affecting experience of a cell adhesion molecule is known, specific inhibitors for cell-cell contact is limited (Jin et al. 2010).

1.2.6.1 Efalizumab

Efalizumab (lymphocyte function-associated antigen-1 inhibitor) is a humanised gG1 mAb that targets the CD11, a chain of the LFA-1 (lymphocyte function-associated antigen).

1.2.6.1.1 Mechanism of Action

Efalizumab attached to lymphocyte function-associated antigen-1 and blocked the lymphocyte function-associated antigen-1-ICAM (intercellular adhesion molecule) interaction to avoid T-cell adhesion, trafficking and onset.

1.2.6.1.2 Pharmacokinetics

Efalizumab offers a certain saturation with 80 per cent modulation of CD11 within a time frame of 24 hours of administration, according to pharmacokinetic and pharmacodynamic studies.

1.2.6.1.3 Therapeutic Uses

Survival of murine skin, heart allografts and psoriasis along with renal transplantation (Sharma and Sharma 2007).

1.2.7 Tolerogens or Inhibitors of Immune Cells

A tolerogen is a foreign antigen that suppresses the immune response or induces immunological tolerance, unlike an immunogen that stimulates an immune response. Instead of inducing the immune system to be active, the tolerogen binds to the lymphocytes' antigen receptor to suppress it.

1.2.8 Inhibitors of Lymphocyte Gene Expression to Reduce Inflammatory Response

1.2.8.1 Mechanism of Action

Cell-cell and cell-cross-section connections are known to expect principal employment to select and establish immune T-cells. Observable among the subnuclear connection parts are integrins (β1 and β2) that intervene in the joint efforts of various invulnerable cells to extracellular systems and other safe cells independently (Adutler-Lieber et al. 2014).

Along with the conventional adhesion molecule, the enzyme ex-vascular adhesion protein 1 (VAP-1) plays a vital role in cell adhesion (Jalkanen et al. 2007). The compound that inhibits leucocyte adhesion, transmigration and expression of associated CAM presents in a therapeutic model for immunosuppressive and anti-inflammatory drugs (Hynes 1992).

Cell adhesion inhibitor will be classified for target for cell-cell adhesion along with expression of cell adhesion molecules (Jia et al. 2015). With impact on expression of cell adhesion molecules is known, specific inhibitors for cell-cell contact are very little (Jin et al. 2010).

1.2.8.2 Therapeutic Uses

Transplant rejection, graft-versus-host disease in bone marrow transplantation, rheumatoid arthritis, SLE and various conditions of skin, asthma, allergic disorders, inflammatory bowel and ophthalmic diseases (Sharma and Sharma 2007).

1.2.8.3 Adverse Effects

Some major effects are growth retardation in minor, avascular bone necrosis, osteopenia, cataract, hyperglycaemia and hypertension.

1.2.9 Inhibitors of Lymphocyte Signalling to Prevent Immune Cell Activation and Proliferation: Calcineurin Inhibitors

1.2.9.1 Cyclosporine

Cyclosporine (cyclosporin A) is a cyclic polypeptide chain with a total of 11 AA produced by the fungal species *Beauvera nivea*. Cyclosporine overpowers T-cell subordinate immune system pathways as transplant rejection and pathway for autoimmunity. It also prevents T-lymphocytes from receiving antigen-triggered signals, effectively reducing the expression of numerous lymphokines, interleukin-2 and anti-apoptotic proteins. Cyclosporine binds to make a complex with cyclophilin, a specific type of cytoplasmic receptor present in target T-cells. This complex binds to calcineurin, inhibiting Ca2+-stimulated dephosphorylation of the cytoplasmic component of the nuclear factor of activated T-cells (NFAT). When NFAT is dephosphorylated and translated, it attaches to the nuclear component required for complete T-cell activation, including the activation of the L-2 and other lymphokine genes. After physical interaction with the cyclosporine/

cyclophilin complex, calcineurin phosphatase activity is stopped. This inhibits NFAT dephosphorylation, resulting in NFAT not entering the nucleus transcription activated and the T-lymphocyte failing to respond to antigenic stimulation.

1.2.9.1.1 Pharmacokinetics

Cyclosporine administered orally or IV. Oral bioavailability is less around 30%. Food stops its absorption. It is metabolised by CYP3A, resulting in drug-to-drug interaction. Inactive metabolite is ejected primarily through the bile and faeces but minimally in urine (Chaudhuri 1997).

1.2.9.1.2 Therapeutic Uses

Organ transplantation, rheumatoid arthritis, psoriasis, early engraftment, extending kidney graft survival and cardiac and liver transplantation (Sengupta 2009).

1.2.9.1.3 Adverse Effects

Renal dysfunction, tremor, hirsutism, hypertension, hyperlipidaemia, gum hyperplasia, hyperuricaemia, hypercholesterolaemia, nephrotoxicity, diabetogenic and increase in LDL cholesterol.

1.2.9.2 Tacrolimus

Tacrolimus (PROGRAF, FK506) is a macrolide antibiotic synthesised by *Streptomyces tsukubaensis*.

1.2.9.2.1 Mechanism of Action

T-cell activation is inhibited via blocking calcineurin. Tacrolimus binds to an intracellular protein FK506-binding protein-12 (FKBP-12), an immunophilin, which is structurally linked to cyclophilin. A complex of tacrolimus-FKBP-12, Ca2+, calmodulin, calcineurin forms and calcineurin phosphatase activity is stopped. As described for cyclosporine, the inhibition of phosphatase activity inhibits dephosphorylation and nuclear translocation of NFAT and stops T-cell activation.

1.2.9.2.2 Pharmacokinetics

Tacrolimus can be administered orally or IV; the liver metabolises 99% by CYP3A and has plasma half-life of 7–8 h (Singhal 2007).

1.2.9.2.3 Therapeutic Uses

Prophylaxis of solid-organ allograft rejection, kidney transplantation and paediatric liver transplantation.

1.2.9.2.4 Adverse Effects

Nephrotoxicity, GI complaints, diabetes, neurotoxicity, hypertension, hyperkalaemia and hyperglycaemia.

1.2.10 Mammalian Target of Rapamycin (mTOR) Inhibitors: Sirolimus

1.2.10.1 Mechanism of Action

Sirolimus blocks T-lymphocyte activation and proliferation downstream of the interleukin-2 and other T-cell growth factor receptors. Sirolimus formation of a complex with immunophilin FKBP-12, but the sirolimus-FKBP-12 complex does not affect calcineurin activity. It binds and blocks protein-kinase targeted mammalian target of rapamycin (mTOR), which is a key protein in cell-cycle progression. Regulation of mTOR stops cell-cycle progression at the G1- to S-phase transition (Goodman 1996).

1.2.10.2 Pharmacokinetics

Oral bioavailability 15% Protein binding 40–45% is against albumin, where it is metabolised by the liver with the help of CYP3A4. Sirolimus excreted 91% through faeces and 2.5% through urine with a plasma half-life of 62 h.

1.2.10.3 Therapeutic Uses

Organ transplant inhibitor is incorporated into stents to inhibit local cell proliferation and blood vessel occlusion.

1.2.10.4 Adverse Effects

Increased level in serum cholesterol, triglycerides, impaired renal function, prolong postponed unite function, lymphocele and anaemia with leucopenia.

1.2.11 Cytotoxic Agents to Reduce Lymphocyte Proliferations

1.2.11.1 Antimetabolites: Azathioprine

Azathioprine (Imuran) is a purine antimetabolite and imidazolyl derivative of 6-mercaptopurine.

1.2.11.1.1 Mechanism of Action

With the exposure to nucleophiles is cleaved to 6-mercaptopurine, which result in conversion to extra metabolites which prohibit de novo purine synthesis. 6-Thio-IMP is changed into 6-thio-GTP, which is incorporated into DNA. Cellular proliferation leads to dysfunction a type of lymphocyte function.

1.2.11.1.2 Therapeutic Uses

Allergenic kidney transplantation and organ transplant rejection.

1.2.11.1.3 Adverse Effects

Bone marrow suppression, leucopenia, thrombocytopenia (not common) and/or anaemia (not common) along with increased susceptibility to infections, hepatotoxicity, alopecia, nausea, vomiting, abdominal pain, mucositis and pancreatitis.

1.2.11.2 Mycophenolate Mofetil

Mycophenolate mofetil (CellCept) is a 2-morpholinoethyl ester of mycophenolic acid (MPA).

1.2.11.2.1 Mechanism of Action

Mycophenolate mofetil is pro-medicate which is hydrolysed into active tranquilise, i.e. mycophenolic acid (MPA) that is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is an integral part in the de novo pathway of guanine nucleotide synthesis. B- and T-lymphocytes are dependent on this pathway, while other cell types use salvage pathway for cell proliferation; MPA therefore selectively inhibits lymphocyte proliferation along with some vital function, i.e. antibody formation and cellular adhesion along with migration (Rang 2007).

1.2.11.2.2 Pharmacokinetics

Mycophenolate mofetil undergoes rapid complete metabolism to MPA after oral/intravenous administration of MPA, which results in metabolising to an inactive phenolic glucuronide MPAG. Out of which 87% is excreted through urine as MPA.

1.2.11.2.3 Therapeutic Uses

Prophylaxis of transplant rejection and renal transplant.

1.2.11.2.4 Adverse Effects

Various adverse effects can be seen, such as leucopenia, diarrhoea, vomiting and sepsis associated with cytomegalovirus (Finkel et al. 2009).

1.2.12 Alkylating Agents

1.2.12.1 Cyclophosphamide

Cyclophosphamide is a unique immunosuppressant, and its function is to enhance T-cell responses despite suppressing B-lymphocyte proliferation.

1.2.12.1.1 Mechanism of Action

Alkylating agents add alkyl groups by forming covalent bonds with nucleophilic moieties ex-phosphate, sulfhydryl, hydroxyl, carboxyl, amino and imidazole groups occuring in DNA/RNA. By forming cross-links between the strands of DNA, they prevent the method of cell division as well as protein synthesis. These drugs are lethal to rapidly reproducing tissues and inducing cell death until they are exposed to the division method. The abovementioned drug's cytotoxicity deals with a degree of DNA alkylation (Goodman 1996).

1.2.12.1.2 Therapeutic Uses

Autoimmune disorder in patients having acquired factor-XIII antibody, bleeding syndromes, antibody-induced unadulterated red cell aplasia and Wegener's granulomatosis.

1.2.12.1.3 Adverse Effects

Pancytopenia, haemorrhagic cystitis, unite-versus-host disease syndrome, nausea, vomiting, cardiac toxicity and electrolyte disturbances (Mythili et al. 2004).

1.2.13 Cytokine Inhibitors (Anticytokine Antibodies)

Tumour necrosis factor-α and IL-1 are pro-inflammatory cytokines found in the pathogenesis of rheumatoid arthritis and Crohn's disease. Activated T-lymphocytes link to the IL-2, swhich promotes its proliferation (Hilmer and Ford 2009).

1.2.13.1 TNF-α Inhibitors

Activated cytotoxic TH1 cells secrete tumour necrosis factor-α that to tumour necrosis factor receptors (TNFR1 or TNFR2) are present in fibroblasts, neutrophils and vascular endothelial cells except for these; there are soluble forms of tumour necrosis factor-α receptor present in serum and synovial fluid. Release of cystine L-1, L-6 and adhesion molecules caused by tumour necrosis factor activation, which promotes leucocyte activation and trafficking (Golan et al. 2011).

1.2.13.2 Etanercept

It's a genetically modified fusion protein made up of two soluble tumour necrosis factor p75 receptors connected to the Fc portion of human-IgG1. The medication works on external administered soluble tumour necrosis factor-α receptor, which provides artificial binding sites to tumour necrosis factor-α, leading to inhibition of tumour necrosis factor-α from attaching to the film-bound TNFR-1 and TNFR-2. The medication is mainly used for treatment of rheumatoid arthritis along with psoriatic arthritis (Saif 2005).

1.2.13.3 Infliximab

It's chimeric monoclonal antibody produced of exposure from mice to human tumour necrosis factor-α. The resultant antibody is fused to constant region IgG-1, which lowers the drug's antigenicity. The medication cross links with film bounded tumour necrosis factor-α receptor on cell surface to block T-cell and macrophage function forcing to stop the release of other pro-inflammatory cytokines. It has longer half-life and does not bind tumour necrosis factor-β. Infliximab is used to treat Crohn's disease and rheumatoid arthritis (Rang 2007).

1.2.13.4 Adalimumab

It is a human recombinant monoclonal antibody to tumour necrosis factor-α, which is significantly less antigenic than infliximab since it lacks the foreign component. Its serum half-life is 2 weeks.

1.2.14 Miscellaneous: Immunostimulants

Indifferent to immunosuppressive agent that blocks the rejection of immune response and autoimmunity, different immunostimulatory drugs are designed with different functionality to infection, immunodeficiency and cancer. They work on both cellular and humoral immune system.

1.2.14.1 Bacillus Calmette-Guerin (BCG)

Live bacillus Calmette-Guerin (BCG: TICE BCG, TheraCys) is made from live culture from the bacillus of Calmette and Guerin strain of *Mycobacterium bovis.*

1.2.14.1.1 Mechanism of Action

At the site of granulomatous reaction.

1.2.14.1.2 Therapeutic Uses

Prophylaxis along with treatment for urinary bladder carcinoma and T1 papillary after transurethral resection.

1.2.14.1.3 Adverse Effects

Shock, hypersensitivity, chills and fever (Goodman 1996).

1.2.14.2 Levamisole

Levamisole (Ergamisol) is manufactured as an anthelmintic yet promises to repair weak immune response.

1.2.14.2.1 Therapeutic Uses

Adjuvant treatment with the help of 5-fluorouracil after surgical resection in patients suffering from Duke's stage C colon cancer and agranulocytosis.

1.2.14.2.2 Adverse Effects

Symptoms related to influenza, nausea, allergic reactions and body ache.

1.2.14.3 Thalidomide

1.2.14.3.1 Mechanism of Action

Thalidomide is proven to lower circulation of tumour necrosis factor-α of patients dealing with erythema nodosum leprosum yet to elevate it in subjects who are HIV seropositive. Indifference to it had been suggested that the medications result in angiogenesis.

1.2.14.3.2 Therapeutic Uses

In rheumatoid arthritis (Heidari 2011).

1.2.14.3.3 Adverse Effects

One of the effects is teratogenicity.

1.2.15 Recombinant Cytokines

Therapeutic uses of recombinant cytokines and their effects (Parnham and Nijkamp 2005; Sharma and Sharma 2007; Katzung 2012):

- Interferons: e.g. alpha, beta and gamma interferons work by induction of various enzymes along with inhibition of cell proliferation, increased phagocytosis by macrophages and augmentation of specific cytotoxicity. They are used in hairy cell leukaemia, malignant melanoma, follicular lymphoma, Kaposi's sarcoma and chronic hepatitis B. They have certain adverse effects such as hypotension, arrhythmias, myocardial infarction, gastrointestinal distress, loss of apetite and weight loss.
- Interleukins: e.g. aldesleukin and des-alanyl-1, serine-125 human IL-2. Cellular immunity is profoundly activated via lymphocytosis, eosinophilia and thrombocytopenia with the release of several cytokines. It has many adverse effects such as capillary leak syndrome, hypotension, reduced organ perfusion and death.

Colony stimulating factors: e.g. filgrastim works by increasing the number and differentiation of myeloid progenitors. It is used in leucopenia and ganciclovir-induced neutropenia. It has many adverse effects such as myocardial infarction and anorexia.

1.2.15.1 Isoprinosine

Isoprinosine aka inosiplex is the complex of the pacetamido-benzoate salt of N, N-dimethylamino-2-propanol and inosine in a molar ratio of 3:1.

1.2.15.1.1 Mechanism of Action

Isoprinosine promises to enlarge production of cytokines as IL-1, IL-2 and IFN-γ. It also increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes.

1.2.15.1.2 Therapeutic Uses

Herpes infections, subacute sclerosing panencephalitis, Epstein-Barr and measles viruses.

1.2.15.1.3 Adverse Effects

Minor CNS depressant and transient nausea along with rise of uric acid in serum and urine (Parnham 2005).

1.2.15.2 Immunocynin

It is a balanced form of haemocynin, which is a non-heme oxygen carrying along copper-containing protein present in arthropods and molluses.

1.2.15.3 Therapeutic Uses

Used to treat some form of urinary bladder cancer.

1.2.15.4 Adverse Effects

Uncommon mild fever. The main three classes of drugs currently utilised for maintenance therapy are antimetabolites, lymphocyte signalling inhibitors and corticosteroids, which are all examples of antimetabolites. Older compounds such as azathioprine and methotrexate as well as more recent compounds such as mycophenolate mofetil and leflunomide are all examples of antimetabolite immunosuppressants. Tamper with critical metabolic pathways in a variety of safe cells, which can stifle their proliferation and induce apoptosis. Azathioprine was the first compound of its kind to be used for immunosuppression in relation to organ transplants. It is a mercaptopurine prodrug and a tranquiliser that interferes with purine nucleic acid metabolism and, as a result, lymphoid cell replication. One major disadvantage of using older drugs such as azathioprine is their lack of specificity and potential for suppressing replication in other highly proliferative tissues, including the bone marrow and stomach. When azathioprine is used in conjunction with allopurinol, increase in drug blood levels is observed (Brooks et al. 1982).

These are the immunosuppressive drugs used for solid organ transplant (Rifle et al. 2005):

- Glucocorticoids inhibit inflammatory gene transcription and induce lipocortins. They are used in maintenance therapy and treatment of acute rejection. They cause hyperglycaemia, osteoporosis, hypercortisolism, growth impairment and impaired wound healing.
- Cyclosporine inhibits IL-2 expression and lymphocyte activation. It is used in maintenance therapy. It causes nephrotoxicity, neurotoxicity, hypertension, hirsutism and gingivital hyperplasia.
- Tacrolimus inhibits IL-2 expression and lymphocyte activation. It is used in maintenance therapy. It causes nephrotoxicity, hypertension, hyperglycaemia, gastrointestinal disturbances and myelosuppression.
- Sirolimus suppresses IL-2 signalling as well as lymphocyte activation. It is used in maintenance therapy and treatment of acute rejection. It causes hypertension, peripheral oedema, hyperlipidaemia and myelosuppression.
- Mycophenolate mofetil inhibits lymphocyte guanosine synthesis. It is used in maintenance therapy and causes hypertension, gastrointestinal disturbances and myelosuppression.

- Azathioprine inhibits purine nucleic acid metabolism. It is used in maintenance therapy. It causes gastrointestinal disturbances and myelosuppression.
- Monoclonal antibodies (e.g. muronomab) inhibit purine nucleic acid metabolism. They are used in maintenance therapy. They cause cytokine release syndrome, pulmonary oedema and hypersensitivity.

These are the immunosuppressive drugs used to treat autoimmune diseases (Libby and Pober 2001):

- Methotrexate inhibits lymphocyte and folate metabolism. It is used in inflammatory bowel disease. It causes nausea, diarrhoea and alopecia.
- Leflunomide is an inhibitor of lymphocyte and pyrimidine synthesis. It is used in rheumatoid arthritis. It causes hepatotoxicity, renal impairment, teratogenic and gastrointestinal disturbances.
- Etanercept, infliximab and adalimumab are TNF-a inhibitors. They are used in rheumatoid arthritis, psoriasis and inflammatory bowel disease. They cause infection and myelosuppression.
- Glucocorticoids inhibit inflammatory gene transcription and induce lipocortins. They are used in rheumatoid arthritis and inflammatory bowel disease. They cause hyperglycaemia, osteoporosis, hypercortisolism, growth impairment and impaired wound healing.

1.3 Conclusion

Immunology, it was reasoned, is presumably the most rapidly developing sector of clinical biotechnology. It's a great way to prevent and cure a variety of problems, including inflammatory skin, gut, respiratory system, joints and specific organ disorders. Immunomodulators would be a major part of medicine in the twenty-first century. Helping the system help itself by enhancing the insusceptible framework is of focal significance in the general public so pushed, horribly supported and presented to poisons that a large portion of us are probably going to have undermined invulnerable frameworks. Immunomodulation, on the other hand may, is a normalising method that corrects feeble invulnerable frameworks and temper insusceptible frameworks that are overactive, yet it does not help the safe framework. Immunomodulators are becoming a viable addition to established modalities, providing a unique methodology for treating incurable diseases in the next decades of the twenty-first century.

Declaration of Conflicting Interests The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

References

Adutler-Lieber S, Zaretsky I, Platzman I, Deeg J, Friedman N, Spatz JP, Geiger B (2014) Engineering of synthetic cellular microenvironments: implications for immunity. J Autoimmun 54:100–111

de Agostino Biella C, Salvador MJ, Dias DA, Dias-Baruffi M, Pereira-Crott LS (2008) Evaluation of immunomodulatory and anti-inflammatory effects and phytochemical screening of Alternanthera tenella Colla (Amaranthaceae) aqueous extracts. Mem Inst Oswaldo Cruz 103(6):569–577

Alamgir M, Uddin SJ (2010) Recent advances on the ethnomedicinal plants as immunomodulatory agents. Ethnomedicine 37(661):227–244

Allison AC (2000) Immunosuppressive drugs: the first 50 years and a glance forward. Immunopharmacology 47(2–3):63–83

Allison AC, Eugui EM (2005) Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. Transplantation 80(2S):S181–S190

Amir GZ, Azad MA, Javidniac K (2007) Haussknechtia elymatica: a plant with immunomodulatory effects. Iran J Immunol 4:26–31

Amirghofran Z, Azadbakht M, Karimi MH (2000) Evaluation of the immunomodulatory effects of five herbal plants. J Ethnopharmacol 72(1–2):167–172

Bafna A, Mishra S (2010) Antioxidant and immunomodulatory activity of the alkaloidal fraction of Cissampelos pareira linn. Sci Pharm 78(1):21–32

Ballarin L (2008) Immunobiology of compound ascidians, with particular reference to Botryllus schlosseri: state of art. Inverteb Surv J 5(1):54–74

Bharani SER, Asad M, Dhamanigi SS, Chandrakala GK (2010) Immunomodulatory activity of methanolic extract of morus alba linn.(mulberry) leaves. Pak J Pharm Sci 23(1)

Bhatt PR, Pandya KB, Sheth NR (2010) Camellia sinensis L: the medicinal beverage: a review. Int J Pharm Sci Rev Res 3(2):6–9

Billiau A, Matthys P (2001) Modes of action of Freund's adjuvants in experimental models of autoimmune diseases. J Leukoc Biol 70(6):849–860

Biswajit D, Suvakanta D, Chandra CR, Jashabir C (2014) An overview of levamisole hydrochloride with immuno-stimulant activity.: 9

Bonacorsi C, Raddi MSG, Carlos IZ, Sannomiya M, Vilegas W (2009) Anti-Helicobacter pylori activity and immunostimulatory effect of extracts from Byrsonima crassa Nied.(Malpighiaceae). BMC Complement Altern Med 9(1):1–7

Bopana N, Saxena S (2007) Asparagus racemosus—ethnopharmacological evaluation and conservation needs. J Ethnopharmacol 110(1):1–15

Brooks RJ, Dorr RT, Durie BG (1982) Interaction of allopurinol with 6-mercaptopurine and azathioprine. Biomed Pharmacother 36(4):217–222

Carlos TM, Harlan JM (1994) Leukocyte-endothelial adhesion molecules.

Chang S-L, Chiang Y-M, Chang CL-T, Yeh H-H, Shyur L-F, Kuo Y-H, Wu T-K, Yang W-C (2007) Flavonoids, centaurein and centaureidin, from Bidens pilosa, stimulate IFN-γ expression. J Ethnopharmacol 112(2):232–236

Chaudhuri SK (1997) Quintessence of medical pharmacology. Indian J Pharm 29(3):206

Chen CF (2007) Aqueous extract of Inonotus obliquus (Fr.) Pilat (Hymenochaetaceae) significantly inhibits the growth of sarcoma 180 by inducing apoptosis. Am J Pharm Toxicol 2:10–17

Cherng J-M, Chiang W, Chiang L-C (2008) Immunomodulatory activities of common vegetables and spices of Umbelliferae and its related coumarins and flavonoids. Food Chem 106(3): 944–950

Cooper JC, Turcasso N (1999) Immunostimulatory effects of beta-1, 3-glucan and acemannan. J Am Nutraceutical Assoc 2:5–10

Costa JFO, David JP, David JM, Giulietti AM, Queiroz LP, Santos RR, Soares MBP (2008) Immunomodulatory activity of extracts from Cordia superba Cham. and Cordia rufescens

A. DC.(Boraginaceae), plant species native from Brazilian Semi-arid. Rev Bras Farm 18(1): 11–15
Dashputre NL, Naikwade NS (2010) Immunomodulatory activity of Abutilon indicum linn on albino mice. Int J Pharm Sci Res 1(3):178–184
Davicino R, Mattar A, Casali Y, Porporatto C, Correa SG, Micalizzi B (2007) In vivo immunomodulatory effects of aqueous extracts of Larrea divaricata Cav. Immunopharmacol Immunotoxicol 29(3–4):351–366
Davtyan H, Ghochikyan A, Hovakimyan A, Petrushina I, Yu J, Flyer D, Madsen PJ, Pedersen LO, Cribbs DH, Agadjanyan MG (2014) Immunostimulant patches containing Escherichia coli LT enhance immune responses to DNA-and recombinant protein-based Alzheimer's disease vaccines. J Neuroimmunol 268(1–2):50–57
De Souza Reis LSL, Frazatti-Gallina NM, de Lima PR, Giuffrida R, Albas A, Oba E, Pardo PE (2008) Efficiency of Matricaria chamomilla CH12 and number of doses of rabies vaccine on the humoral immune response in cattle. J Vet Sci 9(4):433–435
Deshpande JR, Choudhari AA, Mishra MR, Meghre VS, Wadodkar SG, Dorle AK (2008) Beneficial effects of Lagenaria siceraria (Mol.) Standley fruit epicarp in animal models. Indian J Exp Biol 46:234–242
Dias DA, Urban S, Roessner U (2012) A historical overview of natural products in drug discovery. Metabolites 2(2):303–336
Ebringerova A, Hromadkova Z, Hříbalová V, Hirsch J (2002) An immunomodulating pectic arabinogalactan from roots. Chem Pap 56(5):320–325
Elluru S, Duong Van Huyen J-P, Wootla B, Delignat S, Prost F, Negi V-S, Kaveri SV (2007) Tumor regressive effects of viscum album preparations exploration of immunomodulatory mechanisms. Medicina 67:85–89
Ferreira AP, Soares GLG, Salgado CA, Goncalves LS, Teixeira FM, Teixeira HC, Kaplan MAC (2003) Immunomodulatory activity of Mollugo verticillata L. Phytomedicine 10(2–3):154–158
Finkel R, Clark MA, Cubeddu LX (eds) (2009) Pharmacology. Lippincott Williams & Wilkins, pp 33–34
Frech SA, Kenney RT, Spyr CA, Lazar H, Viret J-F, Herzog C, Glück R, Glenn GM (2005) Improved immune responses to influenza vaccination in the elderly using an immunostimulant patch. Vaccine 23(7):946–950. https://doi.org/https://doi.org/10.1016/j.vaccine.2004.06.036
Galeotti M (1998) Some aspects of the application of immunostimulants and a critical review of methods for their evaluation. J Appl Ichthyol 14(3–4):189–199
Gan L, Zhang S-H, Liu Q, Xu H-B (2003) A polysaccharide-protein complex from Lycium barbarum upregulates cytokine expression in human peripheral blood mononuclear cells. Eur J Pharmacol 471(3):217–222
Ganju L, Karan D, Chanda S, Srivastava KK, Sawhney RC, Selvamurthy W (2003) Immunomodulatory effects of agents of plant origin. Biomed Pharmacother 57(7):296–300
Garcon N, Stern PL, Cunningham AL (2011) Understanding modern vaccines: perspectives in vaccinology. Elsevier
Gaur K, Kori ML, Nema RK (2009) Comparative screening of immunomodulatory activity of hydro-alcoholic extract of Hibiscus rosa sinensis Linn. and ethanolic extract of Cleome gynandra Linn. Global J Pharmacol 3(2):85–89
Ghaisas MM, Shaikh SA, Deshpande AD (2009) Evaluation of the immunomodulatory activity of ethanolic extract of the stem bark of Bauhinia variegata Linn. Int J Green Pharm (IJGP) 3(1)
Gohla SH, Zeman RA, Bögel M, Jurkiewicz E, Schrum S, Haubeck HD, Schmitz H, Hunsmann G, Neth RD (1992) Modification of the in vitro replication of the human immunodeficiency virus HIV-1 by TPSg, a polysaccharide fraction isolated from the Cupressaceae Thuja occidentalis L. (Arborvitae). In: Modern trends in human leukemia IX. Springer, pp 140–149
Golan DE, Tashjian AH, Armstrong EJ (2011) Principles of pharmacology: the pathophysiologic basis of drug therapy, 2nd edn. Lippincott Williams & Wilkins
Goodman LS (1996) Goodman and Gilman's the pharmacological basis of therapeutics. McGraw-Hill New York

Gupta A, Gautam MK, Singh RK, Kumar MV, Rao CV, Goel RK, Anupurba S (2010) Immunomodulatory effect of Moringa oleifera Lam. extract on cyclophosphamide induced toxicity in mice. Indian J Exp Biol 48:1157–1160

Habijanic J, Berovic M, Wraber B, Hodzar D, Boh B (2001) Immunostimulatory effects of fungal polysaccharides from Ganoderma lucidum submerged biomass cultivation. Food Technol Biotechnol 39(4):327–332

Halder S, Bharal N, Mediratta PK, Kaur I, Sharma KK (2009) Anti-inflammatory, immunomodulatory and antinociceptive activity of Terminalia arjuna Roxb bark powder in mice and rats.

Hamman JH (2008) Composition and applications of Aloe vera leaf gel. Molecules 13(8): 1599–1616

Heidari B (2011) Rheumatoid arthritis: early diagnosis and treatment outcomes. Caspian J Intern Med 2(1):161

Hilmer SN, Ford GA (2009) General principles of pharmacology. In: Hazzard's geriatric medicine and gerontology. McGraw Hill Medical New York, pp 103–122

Hsu C-H, Sun H-L, Sheu J-N, Ku M-S, Hu C-M, Chan Y, Lue K-H (2008) Effects of the immunomodulatory agent Cordyceps militaris on airway inflammation in a mouse asthma model. Pediatr Neonatol 49(5):171–178

Hung L-C, Lin C-C, Hung S-K, Wu B-C, Jan M-D, Liou S-H, Fu S-L (2007) A synthetic analog of α-galactosylceramide induces macrophage activation via the TLR4-signaling pathways. Biochem Pharmacol 73(12):1957–1970

Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. Cell 69(1): 11–25

Im S-A, Kim K, Lee C-K (2006) Immunomodulatory activity of polysaccharides isolated from Salicornia herbacea. Int Immunopharmacol 6(9):1451–1458

Ismail S, Asad M (2009) Immunomodulatory activity of Acacia catechu. Indian J Physiol Pharmacol 53(1):25–33

Jafarian A, Ghannadi A, Elyasi A (2010) The effects of Allium hirtifolium Boiss. on cell-mediated immune response in mice. Iran J Pharm Res 1:51–55

Jain V, Bhagwat D, Jat RC, Bhardwaj S (2005) The immunomodulation potential of Hyptis suaveolens. Int J Pharm Res Dev 1:1–6

Jalkanen S, Karikoski M, Mercier N, Koskinen K, Henttinen T, Elima K, Salmivirta K, Salmi M (2007) The oxidase activity of vascular adhesion protein-1 (VAP-1) induces endothelial E-and P-selectins and leukocyte binding. Blood 110(6):1864–1870

Jayathirtha MG, Mishra SH (2004) Preliminary immunomodulatory activities of methanol extracts of Eclipta alba and Centella asiatica. Phytomedicine 11(4):361–365

Jeong S, Jeong Y, Yang B, Song C (2006) Chemical characteristics and immuno-stimulating properties of biopolymers extracted from Acanthopanax sessiliflorus. J Biochem Mol Biol 39(1):84

Jia Z, Nallasamy P, Liu D, Shah H, Li JZ, Chitrakar R, Si H, McCormick J, Zhu H, Zhen W (2015) Luteolin protects against vascular inflammation in mice and TNF-alpha-induced monocyte adhesion to endothelial cells via suppressing IKBα/NF-κB signaling pathway. J Nutr Biochem 26(3):293–302

Jiménez-Medina E, Garcia-Lora A, Paco L, Algarra I, Collado A, Garrido F (2006) A new extract of the plant calendula officinalis produces a dual in vitro effect: Cytotoxic anti-tumor activity and lymphocyte activation. BMC Câncer 6(1):119

Jin M, Lee E, Yang JH, Lu Y, Kang S, Chang Y-C, Lee SH, Suh S-J, Kim C-H, Chang HW (2010) Deoxypodophyllotoxin inhibits the expression of intercellular adhesion molecule-1 induced by tumor necrosis factor-α in murine lung epithelial cells. Biol Pharm Bull 33(1):1–5

Kannan M, Singh AR, Kumar TA, Jegatheswari P, Subburayalu S (2007) Studies on immunobioactivities of Nyctanthes arbortristis (Oleaceae). Afr J Microbiol Res 1(6):88–91

Katzung BG (2012) Basic and clinical pharmacology. Mc Graw Hill

Khare CP (2008) Indian medicinal plants: an illustrated dictionary. Springer Science & Business Media

Killestein J, Hoogervorst ELJ, Reif M, Blauw B, Smits M, Uitdehaag BMJ, Nagelkerken L, Polman CH (2003) Immunomodulatory effects of orally administered cannabinoids in multiple sclerosis. J Neuroimmunol 137(1–2):140–143

Kirti S, Mishra NP, Singh J (2004) Tinospora cordifolia, a reservoir plant for therapeutic applicant. Indian J Traditional Knowledge 3:257–270

Kobayashi H, De Mejía E (2005) The genus Ardisia: a novel source of health-promoting compounds and phytopharmaceuticals. J Ethnopharmacol 96(3):347–354

Kobuchi H, Roy S, Sen CK, Nguyen HG, Packer L (1999) Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway. Am J Physiol Cell Physiol 277(3):C403–C411

Kremer JM, Alarcón GS, Lightfoot RW Jr, Willkens RF, Furst DE, Williams HJ, Dent PB, Weinblatt ME (1994) Methotrexate for rheumatoid arthritis. Arthritis Rheum 37(3):316–328

Kumar DSS, Lau CS, Wan JM, Yang D, Hyde KD (2005) Immunomodulatory compounds from Pestalotiopsis leucothes, an endophytic fungus from Tripterygium wilfordii. Life Sci 78(2): 147–156

Labh SN, Shakya SR (2014) Application of immunostimulants as an alternative to vaccines for health management in aquaculture. Int J Fisheries Aquat Stud 2(1):153–156

Leung KN, Leung PY, Kong LP, Leung PK (2005) Immunomodulatory effects of esculetin (6, 7-dihydroxycoumarin) on murine lymphocytes and peritoneal macrophages. Cell Mol Immunol 2(3):181–188

Libby P, Pober JS (2001) Chronic rejection. Immunity 14(4):387–397

Lu Y, Fan J, Zhao Y-P, Chen S-Y, Zheng X-D, Yin Y-M, Fu C-X (2007) Immunomodulatory activity of aqueous extract of Actinidia macrosperma. Asia Pac J Clin Nutr 16(S1):261–265

Madrigal-Bujaidar E, Morales-González JA, Sánchez-Gutiérrez M, Izquierdo-Vega JA, Reyes-Arellano A, Álvarez-González I, Pérez-Pasten R, Madrigal-Santillán E (2015) Prevention of aflatoxin B1-induced dna breaks by β-D-glucan. Toxins 7(6):2145–2158

Mali RG, Hatapakki BC (2008) An in vitro study of effect of Centella asiatica on phagocytosis by human neutrophils. Int J Pharm Sci Nanotechnol 1(3):297–302

Malik JK, Manvi FV, Nanjwade BK, Alagawadi KR, Sanjiv S (2009) Immunomodulatory activity of Gymnema sylvestre R. Br. leaves on in-vitro human neutrophils. J Pharm Res 2(8): 1284–1286

Mathe G (1991) Bestatin, an aminopeptidase inhibitor with a multi-pharmacological function. Elsevier

Meeran SM, Katiyar S, Elmets CA, Katiyar SK (2006) Silymarin inhibits UV radiation-induced immunosuppression through augmentation of interleukin-12 in mice. Mol Cancer Ther 5(7): 1660–1668

Mikhaeil BR, Maatooq GT, Badria FA, Amer MM (2003) Chemistry and immunomodulatory activity of frankincense oil. Z Naturforsch C 58(3–4):230–238

Mishra KP, Padwad YS, Dutta A, Ganju L, Sairam M, Banerjee PK, Sawhney RC (2008) Aqueous extract of Rhodiola imbricata rhizome inhibits proliferation of an erythroleukemic cell line K-562 by inducing apoptosis and cell cycle arrest at G2/M phase. Immunobiology 213(2): 125–131

Mkrtichyan M, Ghochikyan A, Movsesyan N, Karapetyan A, Begoyan G, Yu J, Glenn GM, Ross TM, Agadjanyan MG, Cribbs DH (2008) Immunostimulant adjuvant patch enhances humoral and cellular immune responses to DNA immunization. DNA Cell Biol 27(1):19–24

Mun L, Jun MS, Kim YM, Lee YS, Kim HJ, Seo HG, Lee JH, Son KH, Lee DH, Kim YS (2011) 7, 8-didehydrocimigenol from Cimicifugae rhizoma inhibits TNF-α-induced VCAM-1 but not ICAM-1expression through upregulation of PPAR-γ in human endothelial cells. Food Chem Toxicol 49(1):166–172

Mungantiwar AA, Nair AM, Shinde UA, Dikshit VJ, Saraf MN, Thakur VS, Sainis KB (1999) Studies on the immunomodulatory effects of Boerhaavia diffusa alkaloidal fraction. J Ethnopharmacol 65(2):125–131

Mythili MD, Nair SC, Gunasekaran S (2004) Effect of cyclophosphamide pretreatment on hematological indices of Indian Bonnet monkeys. Indian J Pharm 36(3):175–180
Nadkami AK (2005) Nandkami's Indian Materia Medica. Popular Prakashan, Bombay
Noori S, Naderi G-A, Hassan ZM, Habibi Z, Bathaie SZ, Hashemi SMM (2004) Immunosuppressive activity of a molecule isolated from Artemisia annua on DTH responses compared with cyclosporin A. Int Immunopharmacol 4(10–11):1301–1306
Ordway D, Hohmann J, Viveiros M, Viveiros A, Molnar J, Leandro C, Arroz MJ, Gracio MA, Amaral L (2003) Carpobrotus edulis methanol extract inhibits the MDR efflux pumps, enhances killing of phagocytosed S. aureus and promotes immune modulation. Phytother Res 17(5): 512–519
Oswald IP, Dozois CM, Petit J-F, Lemaire G (1997) Interleukin-12 synthesis is a required step in trehalose dimycolate-induced activation of mouse peritoneal macrophages. Infect Immun 65(4): 1364–1369
Parant M, Audibert F, Parant F, Chedid L, Soler E, Polonsky J, Lederer E (1978) Nonspecific immunostimulant activities of synthetic trehalose-6, 6′-diesters (lower homologs of cord factor). Infect Immun 20(1):12–19
Parnham MJ (2005) Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. Curr Opin Infect Dis 18(2):125–131
Parnham MJ, Nijkamp FP (2005) Principles of immunopharmacology, 2nd edn. Springer
Patel SB, NS NA, Magdum CS (2009) Review on phytochemistry and pharmacological aspects of Euphorbia hirta Linn. Asian J Pharm Res Health Care 1(1)
Patil US, Jaydeokar AV, Bandawane DD (2012) Immunomodulators: A pharmacological review. Int J Pharm Pharm Sci 4(1):30–36
Petrunov B, Nenkov P, Shekerdjiisky R (2007) The role of immunostimulants in immunotherapy and immunoprophylaxis. Biotechnol Biotechnol Equip 21(4):454–462
Pradhan D, Panda PK, Tripathy G (2009) Evaluation of the immunomodulatory activity of the methanolic extract of Couroupita guianensis Aubl. flowers in rats.
Puri A, Srivastava A, Bhardwaj A (2013) Immunostimulant activity of certain plants used in Indian traditional medicine. J Med Plant Res 7(44):3242–3246
Rang HP (2007) Rang and Dale's pharmacology, 6th edn. Elsilver Co, London
Rifle G, Mousson C, Martin L, Guignier F, Hajji K (2005) Donor-specific antibodies in allograft rejection: clinical and experimental data. Transplantation 79(3):S14–S18
Rinku M, Prasanth VV, Parthasarathy G (2009) Immunomodulatory activity of the methanolic extract of Urena lobata Linn. Int J Pharm 7
Ríos J-L (2010) Effects of triterpenes on the immune system. J Ethnopharmacol 128(1):1–14
Sahoo PK, Mukherjee SC (2001) Effect of dietary β-1, 3 glucan on immune responses and disease resistance of healthy and aflatoxin B1-induced immunocompromised rohu (Labeo rohita Hamilton). Fish Shellfish Immunol 11(8):683–695
Saif SR (2005) Pharmacology review for medical students, 1st edn. CBS Publishers & Distributors, New Dehli, Bangalore
Samanta D, Almo SC (2015) Nectin family of cell-adhesion molecules: structural and molecular aspects of function and specificity. Cell Mol Life Sci 72(4):645–658
Satpute KL, Jadhav MM, Karodi RS, Katare YS, Patil MJ, Rub R, Bafna AR (2009) Immunomodulatory activity of fruits of Randia dumetorum Lamk. J Pharmacognosy Phytotherapy 1(3): 36–40
Senchina DS, McCann DA, Asp JM, Johnson JA, Cunnick JE, Kaiser MS, Kohut ML (2005) Changes in immunomodulatory properties of Echinacea spp. root infusions and tinctures stored at 4 C for four days. Clin Chim Acta 355(1–2):67–82
Sengupta PR (2009) Medical pharmacology, 1st edn. CBS Publishers & Distributors
Shah AS, Wakade AS, Juvekar AR (2008) Immunomodulatory activity of methanolic extract of Murraya koenigii (L) Spreng. leaves. Indian J Exp Biol 46:505–509
Sharififar F, Pournourmohammadi S, Arabnejad M (2009) Immunomodulatory activity of aqueous extract of Achillea wilhelmsii C. Koch in mice. Indian J Exp Biol 47:668–671

Sharma HL, Sharma KK (2007) Principles of pharmacology, 1st edn. Paras medical publisher
Sikarwar MS, Patil MB, Sharma S, Bhat V (2010) Aloe vera: plant of immortality. IJPSR 1:7–10
Singh S, Taneja M, Majumdar DK (2007) Biological activities of Ocimum sanctum L. fixed oil—an overview. Indian J Exp Biol 45:403–412
Singhal KC (2007) Essentials of Pharmaco-Therapeutics, 1st edn. CBS Publishers & Distributors
Sirko A, Vaněk T, Góra-Sochacka A, Redkiewicz P (2011) Recombinant cytokines from plants. Int J Mol Sci 12(6):3536–3552
Smit HF (2000) Picrorhiza scrophulariiflora from traditional use to immunomodulatory activity [doctoral thesis]. University of Utrecht, Utrecht, Netherlands
Song SK, Beck BR, Kim D, Park J, Kim J, Kim HD, Ringø E (2014) Prebiotics as immunostimulants in aquaculture: a review. Fish Shellfish Immunol 40(1):40–48
Sredni B, Kalechman Y, Albeck M, Gross O, Aurbach D, Sharon P, Sehgal SN, Gurwith MJ, Michlin H (1990) Cytokine secretion effected by synergism of the immunomodulator AS101 and the protein kinase C inducer bryostatin. Immunology 70(4):473
Steinbach WJ, Stevens DA (2003) Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. Clin Infect Dis 37(Supplement_3):S157–S187
Sugumaran M, Robinson WE (2010) Bioactive dehydrotyrosyl and dehydrodopyl compounds of marine origin. Mar Drugs 8(12):2906–2935
Sunila ES, Kuttan G (2004) Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. J Ethnopharmacol 90(2–3):339–346
Tanaka T, Sugiura H, Inaba R, Nishikawa A, Murakami A, Koshimizu K, Ohigashi H (1999) Immunomodulatory action of citrus auraptene on macrophage functions and cytokine production of lymphocytes in female BALB/c mice. Carcinogenesis 20(8):1471–1476
Thakur M, Bhargava S, Dixit VK (2007) Immunomodulatory activity of Chlorophytum borivilianum Sant. F. Evid Based Complement Alternat Med 4:419–423
Thanh PN, Jin W, Song G, Bae K, Kang SS (2004) Cytotoxic coumarins from the root of Angelica dahurica. Arch Pharm Res 27(12):1211–1215
Tortora Gerard J, Derrickson Bryan H (2008) Principles of anatomy and physiology. Jhon Wiley & Sons, Hoboken, NJ, pp 577–579
Tsuruo T, Naganuma K, Iida H, Yamori T, Tsukagoshi S, Sakurai Y (1981) Inhibition of lymph node metastasis of P388 leukemia by bestatin in mice. J Antibiot 34(9):1206–1209
Vaghasiya J, Datani M, Nandkumar K, Malaviya S, Jivani N (2010) Comparative evaluation of alcoholic and aqueous extracts of Ocimum sanctum for immunomodulatory activity. Int J Pharm Biol Res 1(1):25–29
Varma A, Padh H, Shrivastava N (2011) Andrographolide: a new plant-derived antineoplastic entity on horizon. Evid Based Complement Alternat Med 2011:815390
Vetvicka V (2011) Glucan-immunostimulant, adjuvant, potential drug. World J Clin Oncol 2(2): 115
Wadood A, Ghufran M, Jamal SB, Naeem M, Khan A, Ghaffar R (2013) Phytochemical analysis of medicinal plants occurring in local area of Mardan. Biochem Anal Biochem 2(4):1–4
Wang C, Tao W, Wang Y, Bikow J, Lu B, Keating A, Verma S, Parker TG, Han R, Wen X-Y (2010) Rosuvastatin, identified from a zebrafish chemical genetic screen for antiangiogenic compounds, suppresses the growth of prostate cancer. Eur Urol 58(3):418–426
Zheng W, Chen C, Cheng Q, Wang Y, Chu C (2006) Oral administration of exopolysaccharide from Aphanothece halophytica (Chroococcales) significantly inhibits influenza virus (H1N1)-induced pneumonia in mice. Int Immunopharmacol 6(7):1093–1099
Zvetkova E, Wirleitner B, Tram NT, Schennach H, Fuchs D (2001) Aqueous extracts of Crinum latifolium (L.) and Camellia sinensis show immunomodulatory properties in human peripheral blood mononuclear cells. Int Immunopharmacol 1(12):2143–2150