Natural allergens, photosensitizing agents and fungal toxins. Role of natural products in drug

discovery and development.

Recent developments of natural products used as anticancer agents, antidiabetics, antimalarials

and immunomodulators.

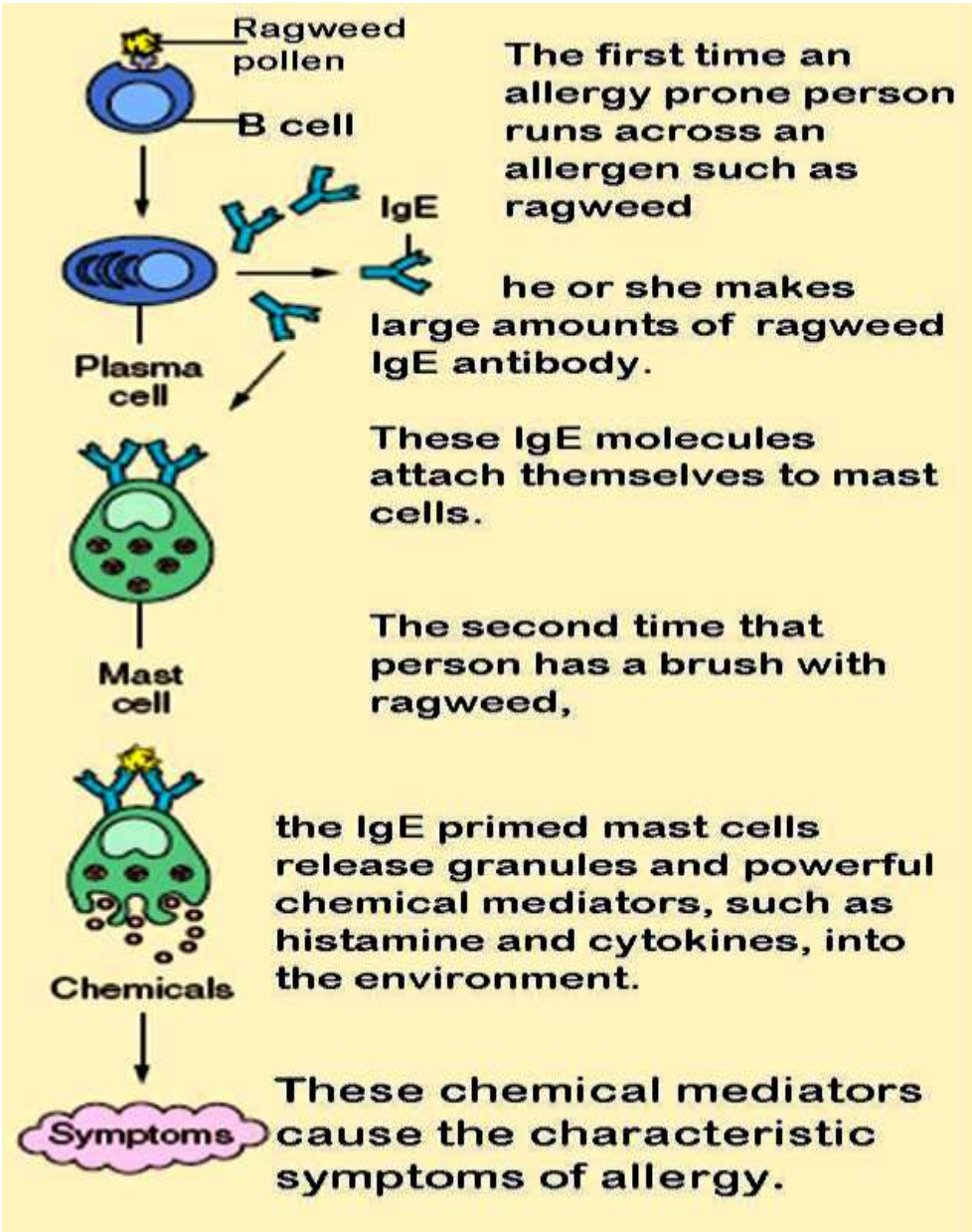
Natural allergens

What are allergens ?

- a substance that causes an allergic reaction.
- Allergens are inciting agents of allergy i.e. The substances capable of sensitizing the body in such a way that an unusual response occurs , in hypersensitive person.
- It may be of **biologic, chemical, or of synthetic origin.**
- The substance such as pollens, dander's, dust etc. as natural allergens.
- Allergens are ***protein or glycoprotein .***

Mechanism

Allergies are abnormal immune system reactions to things that are typically harmless to most people. When you are allergic to something, your immune system mistakenly believes that this substance is harmful to your body. (Substances that cause allergic reactions, such as certain foods, dust, plant pollen, or medicines, are known as allergens.) In an attempt to protect the body, the immune system produces Ig E antibodies to that allergen. Those antibodies then cause certain cells in the body to release chemicals into the bloodstream, such as histamine. The histamine then acts on a person's eyes, nose, throat, lungs, skin, or gastrointestinal tract and causes the symptoms of the allergic reaction. Future exposure to that same allergen will trigger this antibody response again. This means that every time you come into contact with that allergen, you will have an allergic reaction.



TYPES OF ALLERGENS

- Inhalant allergens
- Ingestant allergens
- Ingectant allergens
- Contactant allergens
- Infectant allergens
- Infestant allergens

INHALANT ALLERGENS

- Inhalant allergens are air borne substances as chemicals, causing respiratory disease, inflammation in nose and lungs.
- Inhalant allergies caused by environmental factors such as **pollen, pets, house dust mites and moulds.**
- Inflammation in nose & lungs may cause **Hay fever & Asthma.**

INGESTANT ALLERGENS

- Allergens which are present in **food stuff and swallowed** are termed ingestant (food allergy).
- A food allergy is an immune system response to a food.
- When foods are digested and the nutrients are absorbed, substances in the food (ingestant allergens) **stimulate** allergic response. These reactions cause a number of allergic symptoms.
- Some most common food allergens ingested by patients are milk, egg, peanut, tree nut, fish, shellfish, soy, wheat, orange juice, cod liver oils, etc.

INJECTANT ALLERGENS

- The injectants (***injectable preparations and insects)*** cause allergy in hypersensitive person, allergic conditions is known injectants allergy.
- The natural sources of injectable allergens are produced by the sting of **bees, hornets and wasps.**

CONTACTANT ALLERGENS

- "Any allergens they produce manifestation of hypersensitivity at the site of skin or other mucous".
- A Number of plants products used as additives in cosmetics and perfumes are irritants and cause skin allergy to some hypersensitive individuals.
- Wool fat in cosmetics, soap and soap powders, plain detergents and enzyme detergents, nail polishes, hair dye and hair spray are also included among the major cause of contact dermatitis.

INFECTANT ALLERGENS

- Allergy caused by the metabolic product of living microorganismin the human body.
- The continual presence of certain types of **bacteria, protozoa's, molds, helminths and other parasites in** the body of human being are responsible for chronic infection.
- In such patient bacterial metabolic waste are considered to be infectant allergens.

Types of Reactions

The principal types of reactions observed in Allergy are as follows:

1. **Type 1 reactions:** (immediate type) (anaphylactic): The allergen causes formation of tissue sensitizing antibodies that are fixed to mast cells or leukocytes. On subsequent administration, the allergen reacts with these antibodies activating the cell and causing release of pharmacologically active substances like histamine, leukotrienes etc. and causing effects such as Urticaria, Anaphylactic shock and Asthma. Allergy develops within minutes to hours.
2) **Type II reactions:** (Auto allergy): Where the allergen combines with a protein in the body, so that the body treats it as a foreign protein and forms antibodies.
3) **Type III reactions:** Where antigen and antibody from complexes and activate the compliment. Leukocytes attracted to the site of reaction engulf the immune complexes and release pharmacologically active substances starting an inflammatory response.
4) **Type IV reactions:** They are the delayed type allergy in which antigen- specific receptors produces the T-lymphocytes and subsequent administration will lead to local or tissue allergy like contact dermatitis.

Examples of Plant Allergens

Plant Name	TYPE OF ALLERGY
CATHA EDULIS (KHAT)	Hypertension, constipation
LAWSONIA INERMIS (HENNA)	Chronic inflammation reaction
RICINUS COMMUNIS (CASTOR)	Erythrocyte agglutination,haemorrhagic gastrointestinal irritation,vomiting, profuse watery or bloody purging
CYCAS CIRCINALIS (QUEEN SAGO)	neurodegenerative disorder
CONIUM MACULATUM (HEMLOCK)	Seizures, respiratory depression
*PARTHENIUM (**GAJAR GHANS OR CONGRESS WEED**)*	Dermatitis, respiratory malfunction
CALOTROPIS (MADAR OR AAK OR MILK WEED)	used as an arrow poison, cattle poison, touching the ocular surface may result in Crownflower keratitis
ACKEE (ACHEE OR ACKEE APPLE)	vomiting sickness

Photosensitizing agents

Definition: Drug that are pharmacologically inactive but when exposed to **UV- radiation or sunlight converted to** their active metabolite to produce a beneficial reaction affecting the diseased tissue.

- The photosensitizing agent has property to fluorescence.On exposure to visible light it absorbs a quantum of energy and the molecule becomes activated.
- This energy is transferred to other molecules such as amino acids, histamine, tryptophan and tyrosine, which in turn become activated; subsequently decompose or undergo further chemical reactions.
- Photosensitizing agent are the substance that may leave skin vulnerable to ultraviolet light exposure, causing erythema. Rashes or inflammation
- They are used in leukoderma, increases the formation of melanin pigment.

PSORALEA

- Psoralea corylifolia (Babchi) is an important plant in the Indian Ayurveda and Tamil Siddha systems of medicine.
- The seeds of this plant contain a variety of coumarins including psoralen.
- The seeds have a variety of traditional medicinal used for helping the healing of bone fractures, for lower back and knee pain, impotence, bed wetting, hair loss, and vitiligo, leukoderma.
- **Chemical constituent-** P. corylifolia extract contains a number of chemicalcompoundsincluding flavonoids (neobavaisoflavone, isobavachalcone, bavachalcone,bavachinin, bavachin, corylin, corylifol, corylifolin coumarins(psoralidin, psoralen, isopsoralen and angelicin)andmeroterpenes (bakuchiol and 3-hydroxybakuchiol

Ammi majus

- It is obtained from the fruit of ammi majus (apiaceae)
- **Chemical constituent-** A. majus contains large amounts of the chemicals furanocoumarin, xanthotoxin, and bergapten.
- **Used-** The furanocoumarin can cause phytophotodermatitis and hyperpigmentation and treat vitiligo and psoriasis

SELINUM

It is obtained from the herbs selinum papyraceum.

- Chemical constitutent- xanthotoxin, isopimpinellin, knidlin
- Used- photosensitizing agent

HERACLEUM

- **it is obtained from the root of heracleum candicans.**
- Chemical constitutent- xanthotoxin,
- Used- photosensitizing agent

FUNGAL TOXIN

- **Mycotoxin are chemicals produced by fungi, molds under** certain conditions.
- They are essential for fungal growth and reproduction and toxic to human and animals.
- Disease caused by mycotoxins are called **mycotoxicosis.**
- Disease caused by mold infection are called **mycosis.**
- The reason for the production of mycotoxins is not yet known; they are not necessary for the growth or the development of the fungi. Because mycotoxins weaken the receiving host, the fungus may use them as a strategy to better the environment for further fungal proliferation. The production of toxins depends on the surrounding intrinsic and extrinsic environments and these substances vary greatly in their toxicity, depending on the organism infected and its susceptibility, metabolism, and defense mechanisms.

AFLATOXIN

- Aflatoxin is produced by **Aspergillus parasiticus and A.flavus.**
- There are 5 important aflatoxins called aflatoxin B1,B2,G1,G2 and M.
- Aflatoxins are extremely toxic and their target organ is liver.
- Aflatoxin B1 is three times more toxic than G1 and is the most potent naturally occurring hepatocarcinogen.
- Aflatoxin exposure depresses the immune system and may cause abortion.

STEARIGMATOCYSTIN

- It is produced by certain species of **Aspergillus versicolor.**
- The toxic effects of sterigmatocystin are much the same as those of **aflatoxin B1.**
- It is thus considered as a potent carcinogen,mutagen, and teratogen.
- Toxic effects of sterigmatocystin-fed laboratory animals have included kidney and liver damage and diarrhoea.

ERGOTOXIN

- Ergot or ergot fungi refers to a group of fungi of the genus **Claviceps.**
- The most prominent member of this group is **Claviceps purpurea. This fungus grows on rye and related plants,** and produces alkaloids that can cause **ergotismin** humans and other mammals.
- The neurotropic activities of the ergot alkaloids may also cause hallucinations.
- Ergot cause CNS and peripheral disorders.
- It cause tangerine and abortion in pregnant females.

OCHRATOXIN

- It is produced by **Aspergillus ochraceus and even by penicilium viridicatum .**
- Ochratoxin A has been associated the disease known balkan nephropathy.
- Ochratoxin formation is favoured by cold temperature below 50º F and has been found on cheese cake.
- The target organ seems to be kidney followed by liver.
- Ochratoxin B is non-toxic.

PLANTS AS A SOURCE OF ANTI-CANCER AGENTS

- ***CANCER:-*** *Cancer is characterized by rapid and uncontrolled* formation of abnormal cells which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at other sites.
- **** ANTI-CANCER DRUGS:-*** *The Drugs that are used in inhibiting* the abnormal cell growth or killing the cancer cells.

- Plant-derived compounds have been an important source of several clinically useful anti-cancer agents. These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin, and paclitaxel (Taxol). A Number of promising new agents are in clinical development based on selective activity against cancer related molecular targets, including flavopiridol and combretastin A4 phosphate,

Plant species currently used in clinical cancer treatment

Family	Species	Compound	Target
Apocynaceae	*Vinca rosea*	Ajmalicine, vindoline, catharanthine, vinblastine (VBL), vincristine (VCR), leurosidine.	Leukemia, skin cancer, lymphoma, acute leukemia, breast cancer, lung cancer, brain tumors, Wilms tumors, multiple myeloma, neuroblastoma.
Berberidaceae	*Podophyllum peltatum*	Podophyllotoxins, podophylloresin, diphyllin, etoposide (VP–16), teniposide	Small cell lung cancer, testicular carcinoma, malignant lymphoma, ovarian cancer, neuroblastoma, acute lymphoblastic leukemia, Wilms tumors, brain tumors, urinary tract cancer
	Dysosma pleianthum	Podophyllotoxins	As above
Lamiaceae	*Rabdosia rubescens*	Diterpenoids	Esophaegal carcinoma
Loranthaceae	*Viscum album*	Mistletoe lectins (ML I, II, III), viscotoxins, mistletoe alkaloids	Immunomodulation, complementary therapy
			Breast cancer, colon cancer
Nyssaceae	*Campotheca acuminata*	camptothecin (CPT), topotecan, inotecan	Ovarian, small cell lung cancer, colon cancer, pancreatic cancer
Papaveraceae	*Chelidonium majus*	Alkaloid Ukrain	Immunomodulation Kaposi's sarcoma, astrocytoma
Ranunculaceae	*Paonia alba, P. Lactiflora, P. Suffruticosa*	Root extracts	Intestinal metaplasia and atypical hyperplasia of the gastric mucosa of chronic gastritis
Rubiaceae	*Rubia cordifolia*	Cyclic hexapeptides	Leukemia
Taxaceae	*Taxus baccata*	Taxane diterpenes, (paclitaxel or taxol), cephalomannine	Ovarian cancer, breast cancer, small cell lung cancer
	Taxus brevifolia	10-desacetylbaccatin III	Ags above
	Taxus marei	Paclitaxel, 10- desacetylbaccatin III	As above
	Taxus wallachiana	Paclitaxel, 10-desacetylbaccatin III	As above

RECENT ADVANCES OF NATURAL ANTICANCER AGENTS

1. Natural agents have low toxicity.
2.The MOA of recent natural agents are
* Acts on DNA bases
* Intercalation of DNA
* Inhibit topoisomerases & Proteinkinases
* Induction of Apoptosis (Cell suicide)
3. Many new species are investigated to find out new agents for treatment of cancer.
4.Cell culture techniques are involved to produce new botanical therapeutic agents to treat neoplasms
5. Development of QSAR modelling on anti- cancer agents also produces good therapeutic agents with decreasing toxicity

PLANT-DERIVED ANTICANCER AGENTS IN CLINICAL USE

1. First agents that were clinically used are **Vinca alkaloids, Vinblastine(VLB) & Vincristine (VCR)**, isolatedfromMadagascar periwinkle.
2. Two clinically active agents, **etoposide (VM 26) & teniposide (VP 16-213),** semi synthetic derivatives of epipodophyllotoxin are used in cancer treatment.
3. The use of various parts of **T.brevifolia** and other Taxus species is widely used in caner therapy.
4. Anti-cancer drug **armamentarium** is the class of clinically- active agents derived from **camptothecin**, which is isolated from chinese ornamental tree is widely used.
5. Other plant-derived agents in clinical use are **homoharringtonine (Cephalotaxus harringtonia) and elliptinium,** a derivative of ellipticine, isolated from species of several genera of the Apocynaceae family, including **Bleekeria vitensis A.C.Sm.**

PLANT-DERIVED ANTICANCER AGENTS IN CLINICAL DEVELOPMENT

1.Vinblastine/Vincristine: *Catharanthus roseus/Jamaica,*

Philippines (originally from Madagascar)

2. Etoposide: *Podophyllum species/ Eastern US, Himalayas*
3. Paclitaxel/Docetaxel: *Taxus species/NW US, Europe*
4. Topotecan/Irinotecan: *Camptotheca acuminata/China*
5. *Homoharringtonine: Cephalotaxus harringtonia/China*
6. Flavopiridol: Synthetic based on rohutikine from *Dysoxylum binectariferum/India*
7. *Combretastatins: Combretum caffrum/S. Africa*

PLANTS AS A SOURCE OF ANTI-DIABETICS AGENTS

- Diabetes is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin.
- Types of Diabetes

✓ Type-1 diabetes(insulin dependent)

✓ Type-2 diabetes(insulin independent)

✓ Gestational diabetes

✓ Diabetes due to genetic defects

Medicinal Plants Used For Diabetes

- **Several medicinal plants have found potential use as hypoglycemic in the Indian system of medicines, including Ayurveda.**
- **The use of herbs as hypoglycemics is a major avenue in Indian perspectives particularly for treating diabetes. Example - *Annona squamosa L. Common name: Sugar apple Lowers* blood glucose level.**
- Plant materials have formed the basis for the treatment of diabetes in traditional medicine systems for thousands of years. These medicines for the treatment of diabetes mellitus are probably based mainly on treatment of its obvious symptoms

1. ENHANCE OR PROMOTE INSULIN SECRETION

- Costus speciosus
- Coccinia
- Premna integrifolia Linn
- Spirulina platensis Bridelia ndellensis
- Nephrolepsis tuberosa
- Swetenia mahagoni
- Pterospermum semisagittum
- Momordica charantia

2. INHIBITION OF GLUCOSE ABSORPTION

- Trigonella Foenum Graceum
- Syzgium cumini
- Plantago ovata
- Musa paradisiaca
- Allium cepa
- Pterospermum acerifolium
- Allium sativum
- Costus Specious
- Allium Wallicha Spirulina platensis
- Asparagus racemosus
- Crateava Religiosa
- Ocimum sanctum
- Mangifera indica
- Ipomoea aquatica
- Tamarindus indicus

3. ACTION ON THE PERIPHERAL TISSUES

- Coccinia indica
- Nephrolepsis tuberosa
- Costus speciosus

4. PREVENTION OF ISLET DAMAGE OR POSSIBILITY OF BETA -CELL REGENERATION

- Gymnema sylvestre
- Stephania hernandifolia

5. MIXED ACTIVITY

- Hemidesmus indicus
- Gymnema sylvestre
- Caesalpinia bonducella
- Ocimum sanctum
- Allium sativum

6. IMPROVING INSULIN SENSITIVITY

- Gymnema sylvestre

PLANTS AS A SOURCE OF ANTI-MALARIAL AGENTS

A number of medicinal plants have been used traditionally in the treatment of malaria. Several bioflavonoids from *Selaginella Bryopteris* which includes amentoflavone have been investigated for their anti-protozoal activity in vitro against K strain of *Plasmodium falciparum*. Neem which has nimbolides is used as an antimalarial agent.

Naphthylisoquinoline alkaloids isolated from leaves of *Anastrocladus heyneanus* particularly *anastrocladidine*, *ancistrocladidine ancistrocladinium B* and *ancistrotanzanine* have been shown to exhibit significant anti plasmodial activity. Arteether derived from *artemisinin*, was first isolated from the plant Artemisia annua was approved as antimalarial drugs. Quinine from *Cinchona officinalis* is a potent antimalarial agent.

Plants with Antimalarial Potential

Table 5.2 lists the medicinal plants reported for antimalarial activity:

Table 5.2: List of Nigerian Medicinal Plants Reported for Antimalarial Activity

S. No.	Name of Plant (Family)	Local Name (Hausa)	Parts(s) Used	Type of Assay	Antimalarial Activity
1	*Kaya grandifolia* (Meliaceae)	Madaci	Stem bark	*In vitro*	Good
2	*Lowsonia inermis* (Lythraceae)	Lalle	Leaf	*In vitro*	Fair
3	*Azadirchta indica* (Meliaceae)	Dogon yaro	Stem/leaf	*In vitro*	Good
4	*Zingiber officinale* (Zingiberaceae)	Citta mai yatsu	Root	*In vitro*	Fair
5	*Striga hermonthica* (Scrophul oriaceae)	Kuduji/wuta-wuta	Whole plant	*In vitro*	Very good
6	*Tapinanathus sessillifolia* (loranthaceae)	Kauci	Leaf	*In vitro*	Good
7	*Quassia amara* (simaroubaceae)	Raken giwa	Leaf	*In vivo*	Good
8	*Quassiae undulata* (simaroubae)	Takandar giwa		*In vivo*	Good
9	*Annona senegalensis* (Annonacaea)	Gwandar daji	Leaf	*In vivo*	Good
10	*Cymbogon giganteus* (Poaceae)	Zana	Leaf	*In vitro*	Good/very good
11	*Sarcocephalus latifolius* (Rubiaceae)	Tafashiya	Stem bark/leaf		Good
12	*Morinda morindiodes* (Rubiaceae)	–	Aerial parts/rootbark		Gook
13	*Phyllanthus amara* (Euphorbiaceae)	Baba	Leaf/stem	*In vitro*	Very good
14	*Petivera alliaceae*	–	Stembark/stem	*In vitro*	Good
15	*Mangifera indica* (Anacardiaceae)	Mangwaro	Stem bark/leaf	*In vitro*	Good
16	*Cajanus cajan* (Fabaceae)	Waken suya	Leaf	*In vitro*	Good
17	*Vernonia amygdalina* (Asteraceae)	Shuwaka	Leaf	*In vitro*	Good
18	*Rauwolfia vomitoria* (Apocynaceae)	Wadda	Leaf	*In vitro*	Fair
19	*Cassia fistulosa* (Caesalpniaceae)	–	Stem bark	*In vitro*	Fair
20	*Garcina kola* (Guttiferae)	Namijin goro	Stem bark	*In vitro*	Fair
21	*Chromoleana odorata* (Asteraceae)	–	Aerial parts	*In vitro*	Fair

IMMUNOMODULATORS

- Immune system is a remarkably sophisticated defense system within vertebrates, to protect them from invading agents.
- It is able to generate varieties of cells and molecules capable of recognizing and eliminating limitless varieties of foreign and undesirable agents.
- Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response.
- Thus, immunomodulation is a substance used for its effect on the immune system.
- There are generally of two types immunomodulators based on their effects: immunosuppressant and immunostimulators.
- They have the ability to mount an immune response or defend against pathogens or tumors.

- The potential uses of immunodulators in clinical medicine include the reconstitution of immune deficiency (e.g. the treatment of AIDS) and the suppression of normal or excessive immune function (e.g. the treatment of graft rejection or autoimmune disease).
- Specific immunomodulators administered together with antigens known as immunological adjuvants to boost the immune response to the vaccine constituents.
- For instance, a plant origin saponin used in veterinary medicine. Whereas, the non-specific immunostimulators offer a generalized state of resistance to pathogens or tumors.
- Fungal product cyclosporine A selectively block the function of T lymphocyte and used to prevent graft rejection.

- Different types of agents such as antibiotics, antimetabolites and cytokines may exert an immunomodulation action that is expressed in the augmentation and/or inhibition of different immune responses.
- A number of natural products and synthetic immunopotentiators termed as Biological Response Modifiers (BRMs) are becoming increasingly popular for testing their potential for augmenting immune responses.
- **Immunomodulatory activity of plant derived compounds**

Sterols and sterolins

The phytosterols, β-sitosterol, and its glucoside enhanced the proliferative response of T-cells stimulation.

Immunomodulatory activity of crude plant extracts

1. Fruits of Emblica officinalis
2. Whole plant of Evolvulus alsinoides
3. Ethanolic extract of Acorus calamus rhizome
4. Crude extract of Tinospora cordifolia
5. Ethanolic extract of Boerhaavia diffusa
6. Methanol extract of Eclipta Alba and Centella asiatica
7. An aqueous extract of Rhodiola imbricate
8. Ethanolic extracts Silybum marianum, Matricaria chamomilla, Calendula officinalis, Cichorium intybus and Dracocephalum kitschy
9. Ethanolic extracts Echinacea purpurea
10. Methanol extract of Carpobrotus edulis
11. Alcoholic extract of the fruits (black pepper) Piper longum
12. Ethanolic extract of Boerhaavia diffusa
13. The extract of Apium graveolens
14. Viscum album
15. Cuscuta europea.
16. plant extracts, of Uncaria tomentosa, Hypericum perforatum

THANKYOU