UNIT V

NATURAL ALLERGEN

The untoward immunological reaction to an allergen seen in a patient with defective immune system is called as Allergy. The groups of substances that cause allergic manifestation are called as Allergens.

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.

Allergic reactions can be mild, like a running nose, or they can be severe, like difficulty in breathing. An asthma attack, for example, is also an allergic reaction to something that is breathed into the lungs in a person who is susceptible. Some types of allergies produce multiple symptoms, and in rare cases, an allergic reaction can become very severe - this severe reaction is called **anaphylaxis**. Some of the signs of anaphylaxis are difficulty in breathing, difficulty in swallowing, swelling of the lips, tongue, and throat or other parts of the body, and dizziness or loss of consciousness. Anaphylaxis usually occurs minutes after exposure to a triggering substance, such as a peanut, but some reactions may be delayed by as long as 4 hours. Luckily, anaphylactic reactions don't occur often, and they can be treated successfully if proper medical procedures are followed. The tendency to develop allergies is often hereditary, which means it can be passed down through your genes. A person usually doesn't inherit a particular allergy, just the likelihood of having allergies.

Some of the most common allergens are:

1. Foods: Food allergies are most common in infants and often go away as a child gets older. Although some food allergies can be serious, many simply cause annoying symptoms like an itchy rash, a stuffy nose, and diarrhea. Most allergy specialists agree that the foods that people are most commonly allergic to are milk and other dairy products, eggs, wheat, soy, peanuts and tree nuts, and seafood.

2. Insect bites and stings: The venom (poison) in insect bites and stings causes allergic reactions in many people. These allergies can be severe and may cause an anaphylactic reaction in some people.

3. Airborne particles: These are often called environmental allergens, and they are the most common allergens. Some examples of airborne particles that can cause allergies in people are dust mites (tiny bugs that live in house dust); mold spores; animal dander (flakes of scaly, dried skin, and dried saliva from your pets); and pollen from grass, ragweed, and tree.

4. Medicines: Antibiotics - medications used to treat infections - are the most common types of medicines that cause allergic reactions. Many other medicines, including over-the-counter medications (those you can buy without a prescription), can also cause allergic reactions.

5. Chemicals: Some cosmetics or laundry detergents can cause people to break out in an itchy rash (hives). Usually, this is because the person has a reaction to the chemicals in these products. Dyes, household cleaners, and pesticides used on lawns or plants can also cause allergic reactions in some people.

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.

Treatment of Allergy

The types, causes and contributing factors of allergy are numerous, so the therapy is complex and can be divided into three types:

a. Environmental control to eliminate or minimize exposure to the allergen.

b. Symptomatic drug therapy by use of antihistamines, corticosteroids and sympathomimetic.

c. Specific immunotherapy

Mode of Action

During immunotherapy, there is an increase in antibody, specifically directed against the injected allergen which is primarily Ig G and is the serum factor named as "blocking antibody" by Cooke. It has been reported that the patients who develop higher blocking antibody titres have fewer symptoms than those who develop lower titre values.

Tests Employed to Detect Type - I Hypersensitivity Reactions

1. Prausnitz – Kustner Test (PK-test)
2. Radio Allergo Sorbent Test (RAST)
3. Intra Dermal Test (ID – test)
4. Prick Test
5. Conjunctival Test
6. Basophils Degranulation Test
7. Histamine Release Test.
8. Monkey Ileum Sensitization Test.
9. Provocation Test

The quality of extracts, proper selection of cases, and identification of extract allergens and proper planning of therapy are the requisites of an ideal specific immunotherapy program.

FUNGAL TOXINS.

Mycotoxins are naturally occurring toxins produced by filamentous fungi in many agricultural crops but especially in cereals and most oilseeds both in the field, after harvest and during storage and later when processed into food and animal feed and feed concentrates Mycotoxins occur particularly in regions or countries with climates of high temperature and humidity or where there are poor crop harvesting and storage conditions, which encourage mould growth and mycotoxin development. Human intake of mycotoxins occurs mainly from plant-based foods and from animal-derived foods such milk and milk products and certain fermented meat-based products. Mycotoxicosis is poisoning associated with exposures to mycotoxins and the symptoms depend on the type of mycotoxin, the concentration and length of exposure as well as age, health, and gender of the exposed individual .There is little published information on synergistic effects associated with other factors such as genetics, diet, and interactions with other toxins.

The majority of these toxins are produced by fungi of the genera, Aspergillus, Penicillium and Fusarium. The most commonly occurring mycotoxins include aflatoxins (B1, B2, G1, G2, M1), ochratoxin A, patulin, citrinin, sterigmatocystin and the fusarium toxins namely fumonisins (B1, B2 and B3), zearalenone, T-2 and HT-2 toxins, nivalenol and deoxynivalenol

Some important toxigenic species of filamentous fungi and related mycotoxins

Toxin	Fungal species
Aflatoxins B1, B2, cyclopiazonic acid	Aspergillus flavus

Aflatoxins B1, B2, G1, G2	A. parasiticus
Ochratoxin A; Penicillic acid	A. ochraceus
Sterigmatocystin, cyclopiazonic acid	A. versicolor
Ochratoxin A, citrinin	Penicillium verrucosum
Rubratoxins	P. purpurogenum
Patulin, citrinin	P. expansum
T-2 toxin	Fusarium sporotrichiodes
Fumonisin B1	F. verticilloides
Deoxynivalenol, nivalenol, zearalenone	F. graminearum
Tenuazonic acid	Alternaria alternata
Satratoxins	Stachybotrys atra

MOULD DAMAGED FOODSTUFFS

Mould damaged foodstuffs	Major source	Minor source	Secondary infection
	Cereals	Fruits	Consumer foods
	Herbs, spices, oil seeds	Vegetables	Compounded animal feeds

Residues in animal tissues and animal products	Milk (animal and human	Meats (liver, kidney	Dairy produce

Regulatory limit of aflatoxins in EU and some countries

Country/region	Total aflatoxins (µg/kg)
Australia	5
China	20
European Union	4*
India	30
Kenya	20
US	20

PHOTOSENSITIZING AGENTS

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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.

Following plant are used as photosensitizing agent:

1-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, ba vachalcone,bavachinin, bavachin, corylin, corylifol, corylifolin coumarins(psoralidin, psoralen, isopsoralen and angelicin)andmeroterpenes (bakuchiol and 3-hydroxybakuchiol

2- 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

3-SELINUM – It is obtained from the herbs selinum papyraceum.

Chemical constitutent- xanthotoxin, isopimpinellin, knidlin

Used- photosensitizing agent:

4- HERACLEUM- it is obtained from the root of heracleum candicans.

Chemical constitutent- xanthotoxin,

Used- photosensitizing agent

ROLE OF NATURAL PRODUCT IN DRUG DISCOVERY:

Natural product including plant. Animal, and mineral have been the basis of treatment of human being. Historically the majority of new drug have been generated from natural product (secondary metabolite)

Before 20th century, crude and semi pure extracts of plant, animal, mineral represent the only medication available to treat human and domestic animal illness.

Classical example of drug compound discovered this way are morphine , the active agent in opium, and digoxin, a heart stimulant from flower digitalis lanata. Although traditionally natural products have played an important role in drug discovery, in the past few years most Big Pharma companies have either terminated or considerably scaled down their natural product operations.

One of the next breakthroughs in drug discovery was the use of mechanism-based screening for bioassay-guided fractionation. Through continual improvement of screening formats, reagent production, robotics, and data management, mechanism-based screening has since become themainstay of high-throughput screening (HTS). Some of the first compounds identified in the early 1970s using mechanism-based screening methods included the â-lactamase Inhibitor clavulanic acid from Streptomyces clavuligerus and the HMG-CoA reductase inhibitor mevastatin from Penicillium citrinum.The advent of combinatorial chemistry about 15 years ago created huge excitement in the pharmaceutical industry, and most Big Pharma companies quickly changed their drug discovery strategies to include a significant proportion of combinatorial chemistry. The impending structure of the human genome and the promise of a plethora of new targets added to the excitement of the time. The basic premise was that combinatorial chemistry would generate libraries

consisting of millions of compounds, which wouldbe screened by HTS and produce drug leads compound.

Nature as a source of new drug compound. Natural product have played a key role in pharma reasrch, as many medicine are either natural products or derivative thereof. It is estimated that about 40% of all medicament is either natural product or their semisynthetic derivative. Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were The basis of most early medicines such as 1-aspirin (**1I**),digitoxin (**III**), morphine (**IV**), quinine and pilocarpine

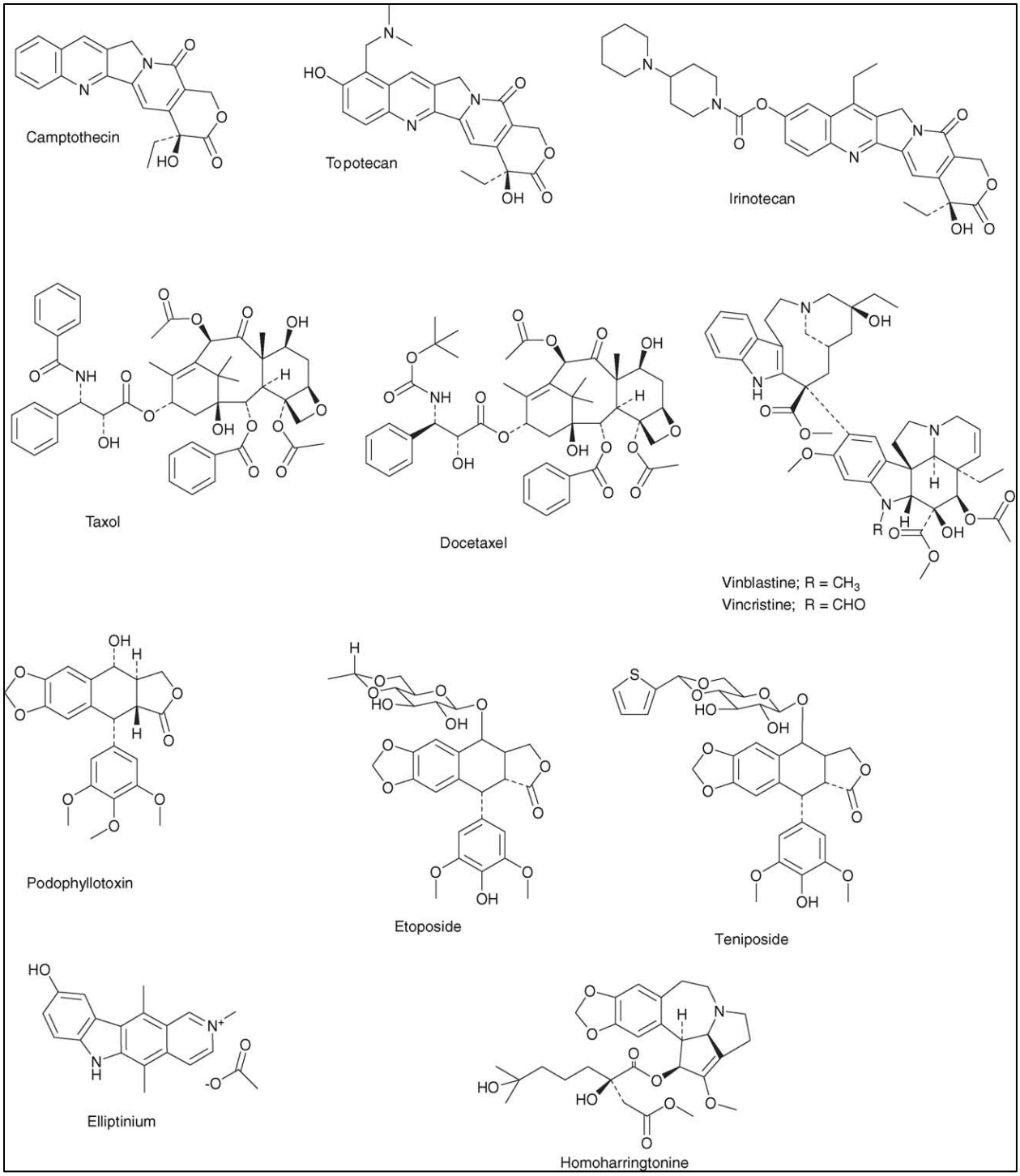
[B] PLANTS AS A SOURCE OF ANTI-CANCER AGENTS

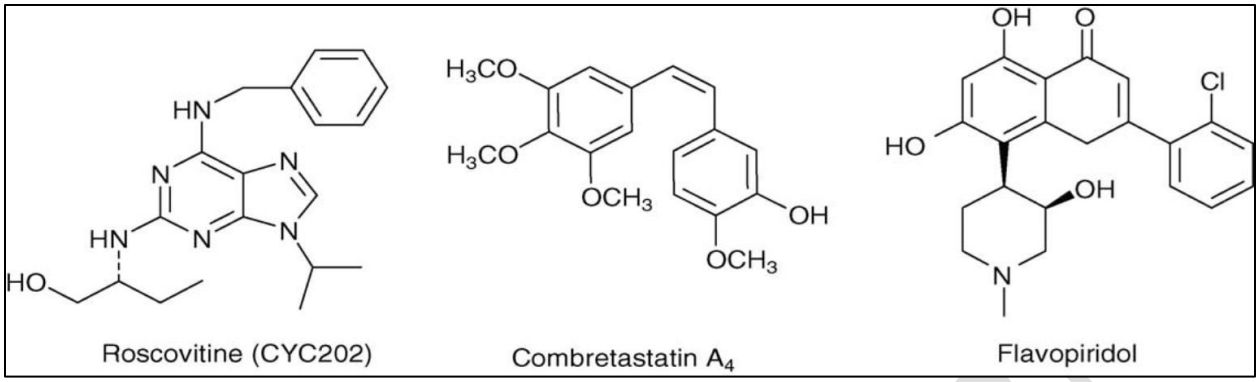
Plant-derived compounds have been an important source of several clinically useful anti-cancer agents. These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin, and paclitaxel (Taxol). A Number of promising new agents are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

Plant-derived anti-cancer agents in clinical use

The first agents to advance into clinical use were theso-called vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the Madagascar periwinkle, Catharanthus roseus

Plant-derived anti-cancer agents


Camptothecin
Topotecan
Irinotecan
Taxol
Docetaxel
Vinblastine; R = CH3
Vincristine; R = CHO
Podophyllotoxin
Etoposide
Teniposide
Elliptinium
Homoharringtonine



[C] PLANTS AS A SOURCE OF ANTI-DIABETICS AGENTS

Medicinal plants play an important role in the treatment of diabetes mellitus, especially in the developing countries due to their cost effectiveness. Diabetes mellitus, a metabolic disorder, is becoming a serious threat to mankind health. The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030. Among all type of diabetes, type 2 diabetes is main complication. Currently available treatment options in modern medicine have several adverse effects. Therefore, there is a need to develop safe and effective treatment modalities for diabetes. In this regard, plants provide the best option for search of desired safe and effective medications. Since ancient times, plants have been an exemplary source of medicine. Various plants have been found to possess significant anti-diabetic property after their preclinical and clinical evaluation. . Use of these plants may delay the development of diabetic complications and can correct the metabolic abnormalities through variety of mechanisms. Moreover, during the past few years many phytoconstituents responsible for anti-diabetic effects have been isolated from plants. Since this review has been presented in a very interactive manner showing geographical region of availability, parts of plant used, mechanism of action and phytoconstituents responsible for particular action, it will be of great importance

Diabetes mellitus is chronic metabolic disorders that affect human body in terms of physical, psychological and social health. It is defined as a group of disorders characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins

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

Possible mechanism of action Name of the plant material

1. ENHANCE OR PROMOTE INSULIN SECRETION

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

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. MIXED ACTIVITY

Hemidesmus indicus
Gymnema sylvestre
Caesalpinia bonducella
Ocimum sanctum
Allium sativum

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

Gymnema sylvestre
Stephania hernandifolia

6. IMPROVING INSULIN SENSITIVITY

Gymnema sylvestre

PLANTS AS A SOURCE OF ANTI-MALARIAL AGENTS

5.4.3.3. Natural Products used as Antimalarials

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	Active Compounds
1	*Kaya grandifolia* (Meliaceae)	Madaci	Stem bark	*In vitro*	Good	NA
2	*Lowsonia inermis* (Lythraceae)	Lalle	Leaf	*In vitro*	Fair	NA
3	*Azadirchta indica* (Meliaceae)	Dogon yaro	Stem/leaf	*In vitro*	Good	NA
4	*Zingiber officinale* (Zingiberaceae)	Citta mai yatsu	Root	*In vitro*	Fair	NA
5	*Striga hermonthica* (Scrophul oriaceae)	Kuduji/wuta-wuta	Whole plant	*In vitro*	Very good	Saponins, tannins
6	*Tapinanathus sessillifolia* (loranthaceae)	Kauci	Leaf	*In vitro*	Good	Saponins, flavonoids
7	*Quassia amara* (simaroubaceae)	Raken giwa	Leaf	*In vivo*	Good	NA
8	*Quassiae undulata* (simaroubae)	Takandar giwa		*In vivo*	Good	NA
9	*Annona senegalensis* (Annonacaea)	Gwandar daji	Leaf	*In vivo*	Good	Alkaloids, tannins cardiac glycosides
10	*Cymbogon giganteus* (Poaceae)	Zana	Leaf	*In vitro*	Good/very good	NA
11	*Sarcocephalus latifolius* (Rubiaceae)	Tafashiya	Stem bark/leaf		Good	NA
12	*Morinda morindiodes* (Rubiaceae)	–	Aerial parts/rootbark		Gook	NA
13	*Phyllanthus amara* (Euphorbiaceae)	Baba	Leaf/stem	*In vitro*	Very good	NA
14	*Petivera alliaceae*	–	Stembark/stem	*In vitro*	Good	NA
15	*Mangifera indica* (Anacardiaceae)	Mangwaro	Stem bark/leaf	*In vitro*	Good	Tannins, terpenoids
16	*Cajanus cajan* (Fabaceae)	Waken suya	Leaf	*In vitro*	Good	NA
17	*Vernonia amygdalina* (Asteraceae)	Shuwaka	Leaf	*In vitro*	Good	NA
18	*Rauwolfia vomitoria* (Apocynaceae)	Wadda	Leaf	*In vitro*	Fair	NA
19	*Cassia fistulosa* (Caesalpniaceae)	–	Stem bark	*In vitro*	Fair	NA
20	*Garcina kola* (Guttiferae)	Namijin goro	Stem bark	*In vitro*	Fair	NA
21	*Chromoleana odorata* (Asteraceae)	–	Aerial parts	*In vitro*	Fair	NA

[D] 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. Immunopharmacology is a comparatively new and developing branch of pharmacology aims at searching for immunomodulators. 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). Recent advances on the ethno medicinal plants as immunomodulatory agents. 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. Medicinal plants and their active components have been shown to be an important source of immunomodulators.

Macrophages are quiescent cells which get activated when stimulated. 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 responsesA 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. Among the natural BRMs many herbs and medicinal plants have long been known for their immunoaugmentary potential

Immunomodulatory activity of crude plant extracts

S.N.	**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

Immunomodulatory activity of plant derived compounds

Sterols and sterolins

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