Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2020.v09.i02.A08

NATURAL PRODUCTTS AND MEDICINAL PLANTS: BOOSTING IMMUNE SYSTEM AGAINST COVID-19 AND OTHER VIRUSES

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ABSTRACT

In 2019, the COVID-19 pandemic caused by SARS-CoV-2 in Wuhan, China and raised a worldwide fear with no effective treatment or protection. Therefore, all researchers are racing to provide a solution to this catastrophe either via vaccination or drug development or drug repurposing. Regardless the high fatalities associated with (COVID-19) pandemic, many studies have shown that persons with strong immune systems are more likely not to be infected with the virus or even if they get infected, they have higher chances of surviving the scourge. Until now, several local herbs have been shown to have antibacterial and antiviral properties. Although there are no cures for the flu viruses including coronavirus, researchers suggest many natural remedies can ease the symptoms. They have been shown to provide relief and prevent viral infections. Earlier, The liver research laboratory (FAB-Lab, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt) presented several approaches for a better utilization of natural products as potential antiviral; Anti-herpes (Badria *et al*, 2003)[1] and immunomodulators (Mikhaeil *et al*, 2003)[2]. Here we present a comprehensive review on the chemistry, biology, and therapeutic applications of many natural products as possible therapy and/or prophylactic for many viral diseases including COVID-19.

KEYWORDS

COVID-19, FAB-Lab, Immunomodulators and Natural Products.

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INTRODUCTION

The liver research laboratory (FAB-Lab, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt) presented several approaches for a better utilization of natural products as potential therapeutic agents including the following,

- Anti-herpes activity of isolated compounds from frankincense (Badria *et al*, 2003)[3].

- Chemistry and immunomodulatory activity of frankincense oil (Mikhaeil *et al*, 2003)[2].
- Mirazid: a new schistosomicidal drug (Badria *et al*, 2001)[4].
- Is man helpless against cancer? An environmental approach: antimutagenic agents from Egyptian food and medicinal preparations (Badria, 1994)[5].
- Free-B-Ring flavonoids as potential lead compounds for colon cancer therapy (Ibrahim *et al*, 2014)[6].
- Immune-modulatory potentials of anti-neoplaston A-10 in breast cancer patients (Badria *et al*, 2000a)[7].
- Potential utility of anti-neoplaston A-10 levels in breast cancer (Badria *et al*, 2000b)[8].

There are number of examples which deal with enzymes as drug targets involved in the designing of enzyme inhibitors from commonly available natural products, such as;

- Olive and ginkgo extracts as potential cataract therapy with differential inhibitory activity on aldose reductase (Elimam *et al*, 2017)[9].
- Flavonoids containing an alpha-keto group as a new type of tyrosinase inhibitors from natural products as potential treatments for hyperpigmentation (Badria, 2001)[10].
- Cycloartane Glycoside: A New Lactate Dehydrogenase Inhibitor, from the Aerial part of Agriculture Waste of Watermelon (El-attar *et al*, 2015)[11].

Later, modulation of different biological activities via semi-synthesis of commonly available natural products was extensively studied by Badria's group including the following,

- Betulinic acid analogues as potent topoisomerase inhibitors (Abdel Bar *et al*, 2009)[12].
- Synthesis, Docking, Cytotoxicity, and LTA4H Inhibitory Activity of New Gingerol Derivatives as Potential Colorectal Cancer Therapy (El-Naggar *et al*, 2017)[13].
- Design and pharmacophore modeling of bi-aryl methyl eugenol analogs as breast cancer invasion inhibitors (Abdel Bar *et al*, 2010)[14].
- Approach for chemosensitization of cisplatin-resistant ovarian cancer by cucurbitacin B (El-Senduny *et al*, 2016)[15].
- Derivatization, molecular docking and *in vitro* acetyl cholinesterase inhibitory activity of glycyrrhizin as a selective anti-Alzheimer agent (Abdel Bar *et al*, 2019)[16].

All of the previous examples are about using one compound that targets single enzyme (the on-target approach), with high selectivity to prevent any undesired effects from mis-targeting the other targets (the off-targets). Previously it was undesirable for drugs to inhibit many targets, because of the adverse effects. Though, the complexity of the current hopeless pathologies has demonstrated clearly that such single-target drugs are insufficient to achieve a therapeutic effect. In parallel, it was found that molecules targeting more than one protein may have a safer profile when compared to the single-targeted (Ramsay *et al*, 2018)[17], (Badria and Ahmed, 2018)[18].

Detection as well as elimination relay on bonding of immune cellular surface receptors as well as chemical binding to pathogens to trigger complex interaction of signaling of immune response.

Innate immune system is a term which describes the part of the immunity which is present since born; that is, it does not acclimatize to particular pathogens (c.f. Adaptive immunity). It is the first line of defense, to give the other immune arm, adaptive immunity, time to construct a precise response. Innate immune system relay primarily on complement "chemical response system", and the phagocytic/ endocytic systems, that involve roaming of scavenger cells, mainly macrophages, which detect / engulf foreign molecules and pathogen, maintain clearance of debris and pathogens.

On the other hand, adaptive immune system consists mainly of specific white blood cells, lymphocytes that circulate throughout the entire body via blood circulation as well as lymph

systems. The name is due to its nature of adaptation or learning how to recognize and detect specific type of pathogen, as well as retaining a memory to speed up faster response on future exposure. The primary response (from which the cells learn) is slow, often becomes apparent after several days of the initial infection, and may take up weeks to clear pathogen. After that, the immune system gain memory (learned) of that specific kind of causative pathogen. If the body, again, got infected by the same pathogen, the adapted immune system remembers it, and so produces more rapid and efficient responses, called secondary responses. This response is fast enough to produce no clinical manifestations. This memory can be temporary or may persist up to life-time.

Cellular immunity (Cell-mediated) is the simple or complex actions, reactions and interactions of many leukocyte activities. This type depends mainly on T (Thymus) lymphocytes, responsible for the delayed immune response. The T-cells is sensitized by its first exposure to an antigen. Humoral immunity (Antibody-mediated) is the defense mechanisms achieved through circulating antibodies which are secreted by B (Bone cell) lymphocytes. This type of immunity is the antigen-antibody response (Hofmeyr, 2001[19], Organ, 2009)[20].

Organs of the Immune System, (Janeway, *et al*, 2005)[21]

Bone Marrow

All types of immune cells primarily originate from the bone marrow stem cells through a process of hematopoiesis. These cells either mature or migrate as precursors cells to achieve maturation elsewhere. The bone marrow produces immature thymocytes, B-cells, granulocytes and natural killer in addition to red blood cells and platelets.

Thymus

Thymus is the organ in which thymocytes (prothymocytes) achieve maturation in a process referred to as "thymic education". Beneficial T cells are spared, while T-cells that may evoke autoimmunity are eliminated. The mature "educated/selected" T-cells are then released into the circulation.

Spleen

The spleen is the blood immunologic filter. It consists of macrophages, natural killer cells, dendritic cells, T-cells, B-cells and red blood cells. It captures and filters foreign antigens from the blood present them to effector cells as well as B-cells activated to produce antibodies in large amounts. In spleen, old red blood cells are destroyed.

Lymph nodes

The lymph nodes also function as filter for the lymph fluid that drains from most of body tissues. Lymph nodes spread throughout the body and consists mainly of T- and B-cells, macrophages and dendritic cells.

Cells of the Immune System

Origin and types of immune system cells are illustrated in Figure No.1 and are classified as follows:

T-Cells

There are two major subsets of T-cells that are functionally and phenotypically different. The T-helper (CD4+), which is immune coordinator, its main function is to potentiate immune responses by secreting specialized cytokines which activate other white blood cells. T-killer/suppressor subset (CD8+) is the other type of T-cell which is important in direct killing of viral-infected cells, certain tumor cells, and some parasites as well as down-regulation of over immune responses. T-cells often depend on the lymph nodes and spleen as a site of activation, they also present in other body tissues such as lung, liver, intestinal and reproductive tracts and blood circulation.

B-Cells

Antibodies production is the major function of B-lymphocytes. Antigen-antibody reaction is critical mean for signaling to other cells to kill, engulf or remove that substance from the body.

Natural Killer Cells

Natural killer cells, (NK-cells), are similar to the killer T-cell subset (CD8+ T-cells) that directly kill certain tumors and viral-infected cells. NK-cells differ from CD8+ in that they do not need prior lymphoid organ conference before killing.

Activated NK-cells (by CD4+ cytokines) will produce their action more effectively.

Granulocytes [Polymorph-nuclear (PMN)] Leukocytes

Granulocytes are divided into three cellular types depending on their dyes' staining characteristics to Basophils, Eosinophils and Neutrophil. These cells remove pathogen from the body via engulfment degradation using specific enzymes.

Macrophages

Macrophages known as scavengers and antigen-presenting cells (APC) due to their action of picking up and ingestion of foreign materials then present them to other immune system such as B-cells and T-cells. Macrophages upon stimulation exhibit increased phagocytosis and also secretions.

Dendritic cells

Unfortunately, there is little information about dendritic cells as they are hard to be isolated. Recently, dendritic cells were found to bind high amount of AIDS virus, and may act as a reservoir that is during an activation event is transmitted to CD4+ T cells.

Cytokines, category of small proteins, are of major importance in cell signaling. Cytokines comprise interferons, interleukins, chemokines, lymphokines and tumor necrosis factor but generally not hormones nor growth factors. They are remarkably important in the immune system; they regulate the growth, maturation, and responsiveness of specific cell populations and harmonize between humoral and cell-based immune responses. Cytokines are released by special cells as macrophages, T-lymphocytes B-lymphocytes, and mast cells, as well as fibroblasts, endothelial cells, and various stromal cells. They either affect the behavior of other cells, or even the releasing cell itself. More than one type of cell can produce the same cytokine to act through receptors. Also, cytokines may inhibit or enhance other cytokines' action in complicated manners.

Milk thistle has been proven to increase humoral and cellular activity (Wilasrusmee *et al*, 2002)[22]. Ginseng enhances production of macrophages, B and T cells (Liou *et al*, 2004)[23]. Echinacea is being tested as an immune stimulant (Melchart *et al*, 1994)[24].

Because of cytokines importance in the immune system, their modulation by natural products may produce crucial effects on immunity of the host leading to enhancement of its defensive mechanisms. Figure No.2.

Understanding plant based drug immunological profile is key of interest. The effect may be antagonistic, since administration of high doses of an agent tends to suppress the immunity while the same in low doses might become immunostimulant. Also, in some cases the agent may be immunosuppressive and in other case it tends to be immunostimulatory. (Billiau and Matthys, 2001)[25]. Immunomodulator can be used as an alternative to conventional chemotherapy for a variety of diseases especially under the conditions of immune-impairment. Medicinal plants are a rich source of molecules that are claimed to induce non-specific immunomodulation. To regulate the normal immunological function, both stimulation and suppression need to be regulated so to normalize patho-physiological processes, hence the name 'immunomodulatory agents'. It is important to note that, there are limitations to the use of such agents, due to increased risk of infection as well as generalized or uncontrolled effect throughout the immune system. (Killestein *et al*, 2003[26], Ordway *et al*, 2003)[27].

Due to toxicity, low efficacy and elevated cost of synthetic agents, the search for more effective and safer natural immunomodulators is becoming a field of major interest all over the world.

Several medicinal plant extracts used in traditional medicines have shown to be immunomodulators. Some of medicinal plants that exhibit immunomodulatory activities are presented in Table No.1.

Immunomodulatory natural products

Several molecules with immunomodulatory action have been also reported. Various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins and sterols) exhibit a wide

range of immunomodulating activity, (Ganju *et al*, 2003)[67].

Glycosides

Glycosides are plant or animal derived organic compounds that upon enzymatic or acid hydrolysis, yield one or more sugar moieties. There are number of glycosides that have immunomodulatory activities; iridoids and anthraquinone glycosides (Mehrotra *et al*, 2002)[97] as shown in Figure No.3.

Flavonoids

Many flavonoids retains immunomodulatory effect; e.g. eupalitin and centaureidin (Davis and Kuttan, 2000)[98], (Bhattacharya *et al*, 2000)[99]. Figure No.4.

Coumarins

Coumarinsare benzo-α-pyrone derivatives (Makare *et al*, 2001)[100]. Some coumarins exert immunomodulation effects. Example 6, 7-dihydroxycoumarin (Esculetin) which is a coumarin derivative isolated from many medicinal plants such as *Citrus limonia, Artemisia capillaries*, and *Euphorbia lathyris*. It is known to exhibit other diverse biological activities including free radical scavenging, tyrosinase-inhibition, lipoxygenase-inhibitory activity, suppressive activity on oxidative damage to DNA, and cancer chemo-prevention / antitumor activities (Leung *et al*, 2005)[101], Figures No.5.

Alkaloids

Alkaloids are organic nitrogenous compounds that have alkali like behavior (basic nature), hence the name, normally heterocyclic, limited in distribution and have special and wide range of effects on body physiological functions including immunomodulatory activities (Leung *et al*, 2005)[101]. As an example, *Murraya koenigii, Achillea millefolium, Actinidia macrosperma* and *Cissampelos pareira*, Figure No.6.

Thiosulfinates are organic sulfur compounds containing the linkage R-S (O)-S-R. They exert potent immunomodulatory and adaptogenic properties, e.g., Allicinthiosulfinates derived from *Allium hirtifolium* (Jafarian *et al*, 2010)[102]. Figure No.7.

Polysaccharides

Polysaccharides from botanical sources exhibit versatile beneficial therapeutic properties, it is believed that these effects are due to the modulation of innate immunity especially macrophage function. So, the assay and testing of plant polysaccharides provides a special approach to discover novel adjuvants and therapeutic agents that produce desired immunomodulation. The enhancing effect of polysaccharide on lymphocyte proliferation was correlated to its effect on intracellular calcium ions (Ca^{2+}) delivery. *Salicornia herbacea* extract showed to be able to activate monocytic cells and induced its differentiation into macrophages (Alamgir and Uddin, 2010)[103] (Rios, 2010)[104], Figure No.8.

Volatile oils, monoterpenes and sesquiterpenes

Terpenes and terpenoids are mainly volatile oils (Rios, 2010)[104]. A lot of volatile oils exhibit immunomodulatory activity, e.g., eugenol from *Ocimum sanctum*, Figure No.9.

Diterpenes

The immunomodulatory activity of andrographolide, a diterpene isolated from *Andrographis paniculata* has been also reported, Figure No.9.

Saponins and triterpenes

Triterpenoidal saponins may produce immunomodulatory effects, such as those isolated from *Glycyrrhiza glabra* and *Boswellia* spp. (Badria *et al*, 2003)[1], Figure No.10.

Semisynthetic glycyrrhetinic acid derivatives

Semisynthetic modifications are done either to improve potency, enhance pharmacokinetics or to change pharmacodynamics of a lead molecule.

Glycyrrhizin is a triterpenoidsaponin glycoside that contains two molecules of glucuronic acid as glyconepart. Its derivatization may lead to enhancement of its already existing activities or development of newer ones. Glycyrrhetinic acid comprises three main functionalities which can be considered as a main target of simple modifications, 3-hydroxyl group that is involved in glycoside formation, 11-α,β-unsaturatedketone group and 30-carboxylic group.

Several modifications have been done which will be discussed below under Figure No.11, to review the modification and its significance on the main derivative of glycyrrhizin, glycyrrhetinic acid "the aglycone of glycyrrhizin".

Modifications made on position 3-hydroxy (R_1-A ring)

Hydroxylation

Addition of two hydroxyl groups at positions C-1 and C-2 produced trihydroxylated derivatives which showed markedly enhanced antibacterial activity against G +vestrains even more potent than the positive controls (Huang *et al*, 2016)[105].

Acylation

Introduction of acetyl group using acetylating agents as acetic anhydride produced chemical protection of hydroxyl group, and increased lipophilicity of the molecule (Terasawa *et al*, 1992)[106]. 3-Acetyl-18β-glycyrrhetinic acid showed significant curative effect for the treatment of gastric and duodenal ulcer (Zhang *et al*, 2012)[107].

Acylation with di-carboxylic acid as succinic acid affected promotion of anti-tumor activity (Terasawa *et al*, 1992)[106].

Oxidation

Formation of 3-oxo moiety slightly increased lipophilicity which intern produced higher anti-tumor-promoter activity. (Terasawa *et al*, 1992)[106].

Modifications made on position 30-carboxyllic acid (R_2)

Esterification

Methyl glycyrrhetinate has been synthesized by hydrothermal method with glycyrrhizic acid as a precursor. The main purpose of such methylation is protection of carboxylic acid moiety and increase hydrophobic character of the compound. (Zhang *et al*, 2010)[108].

Glycyrrhizin penta-*O*-nicotinate "Niglizin" inhibited HIV-1 and HIV-2 in the model of the chronic infection *in vitro* (Baltina, 2003)[109].

The anti-inflammatory activity of penta-*O*-(4-nitro) benzoate and penta-*O*-cinnamate was more pronounced in the carrageenan and formaldehyde induced models of inflammation in mice (Baltina, 2003)[109].

Amidation

Glycyrrhizin containing cysteine-moiety of "Cys(Bzl) and Cys(Bzl)-Val" residues attached to the glycone part of the molecule stimulated the primary response of immune system and the reaction of mice delayed-type hypersensitivity. (Kondratenko *et al*, 2004)[110].

Glycyrrhizin heterocyclic amide and ureids were more potent and less toxic anti-inflammatory agents in comparison to prednisolone in the mice inflammation induced by formaldehyde and carrageenan (Baltina, 2003)[109].

Glycopeptide and dipeptide derivatives of glycyrrhizin, methyl esters of amino acids (AlaOMe, LeuOMe, GluOMe- OMe), were found immunomodulators that stimulated the primary immune response in mice in the model of delayed-type hypersensitivity (Baltina, 2003)[109].

Modifications made on position 11-α,β unsaturated-ketone (R_3)

11-Oxo group is the chief reason for the apoptotic effect of glycyrrhetinic acid and its derivatives (Csuk *et al*, 2011)[111].

11-Deoxoglycyrrhetinic acid and its salt were used as immune modulators, anti-inflammatory agentsand antiulcer agents (Nakashima *et al*, 1987)[112].

11-Deoxyglycyrrhetinic amide and 3-amino-11-deoxyglycyrrhetinic acid exhibited significant effects on treatment of ulcers, and anti-inflammatory against aseptic arthritis of various animals (Zhang *et al*, 2012)[107].

Table No.1: Some common plant-derived immunomodulators

S.No	Botanical name	Part used	Active constituents	Other biological activities	Ref.
1	*Achillea millefolium* (Asteraceae)	Leaves	Flavonoids, alkaloids, coumarins, triterpenes	Anti-inflammatory, antispasmodic, antipyretic, diuretic.	(Sharififar *et al*, 2009)[28]
2	*Aloe vera* Tourn (Liliaceae)	Gel from leaves	Anthraquinone glycosides	Purgative, emmenagogue, emollient, ant-inflammatory.	(Hamman, 2008[29], Sharififar *et al*, 2009)[28]
3	*Andrographis paniculata* (Acanthaceae)	Leaves	Diterpenes	Hepatoprotective, antispasmodic, blood purifier, febrifuge.	(Varma *et al*, 2011)[30]
4	*Abutilon indicum* (Malvaceae)	Whole plant	Flavonoids, triterpenoids	Diuretic, antibacterial.	(Dashputre and Naikwade, 2010)[31]
5	*Asparagus racemosus* (Liliaceae)	Roots	Saponins, sitosterols	Ulcer healing agent, nervine tonic, anti-gout.	(Bopana and Saxena, 2007)[32]
6	*Allium hirtifolium* (Alliaceae)	Herb	Thiosulfinates, flavonoids	Anti-rheumatic, anti-inflammatory.	(Dashputre and Naikwade, 2010)[31]
7	*Alternanthera tenella* (Amaranthaceae)	Herb	Flavonoids, triterpenes	Antitumor, anti-inflammatory.	(Guerra *et al*, 2003)[33]
8	*Actinidia macrosperma* (Actinidiaceae)	Fruits	Alkaloids, saponins	Anti-leprotic.	(Lu *et al,* 2007)[34]
9	*Acacia catechu* (Leguminosae)	Leaf	Flavonoids, quercetin	Hypoglycaemic, astringent.	(Ismail and Asad, 2009)[35]
10	*Acanthopanax sessiliflorus* (Araliaceae)	Shoots and roots	Biopolymers	Lympho-proliferative activity.	(Jeong *et al*, 2006)[36]
11	*Agelas mauritianus* (Porifera)	Sponge	Glycolipid	Phagocytotic activity.	(Hung *et al*, 2007)[37]
12	*Aphanothece halophytica* (Chroococcales)	Cyano bacterium	Exopolysaccharide	Inhibits influenza virus.	(Zheng *et al*, 2006)[38]
13	*Apium graveolens* (Apiaceae)	Leaves, seeds	Flavonoids, coumarins	Anti-inflammatory.	(Cherng *et al*, 2008)[39]
14	*Ardisia* spp. (Myrsinaceae)	Shrub, Branches and leaves	Peptides, saponins, Isocoumarins, quinones and alkyl phenols	Anti-metastatic drug, anti-HIV property.	(Kobayashi and De Mejia, 2005)[40]
15	*Aristolochia* spp. (Aristolochiaceae)	Leaves	Aristolochic acid	Antiangiogenic, employed in prostate cancer.	(Wang *et al*, 2010)[41]

16	*Artemisia annua* (*Compositea*)	Herb	Artemisinin	Immunosuppressive	(Noori *et al*, 2004)[42]
17	*Aspergillus* spp. (Trichocomaceae)	Fungus	Polyene, triazole	Anti-fungals.	(Steinbach and Stevens, 2003)[43]
18	*Boswellia* spp. (Burseraceae)	Gum resin	Triterpenes (ursanes)	Hypoglycaemic.	(Mikhaeil *et al*, 2003)[2]
19	*Bauhinia variegate* (Caesalpiniaceae)	Roots, bark, buds	Flavonoids, beta-sitosterol, lupeol	Anti-fungal, astringent.	(Ghaisas *et al*, 2009)[44]
20	*Botryllus schlosseri* (Botryllidae)	Tunicates	Cytokines	Anti-oxidant, anti-viral, anti-microbial and anti-tumoral.	(Ballarin, 2008)[45]
21	*Bidens pilosa* (Asteraceae)	Flowers, leaves	Polyacetylenes	Anti-inflammatory, immunosuppressive, antibacterial and antimalarial.	(Chang *et al*, 2007)[46]
22	*Boerhaavia diffusa* (Nyctaginaceae)	Herb	Alkaloid	Immunostimulatory.	(Mungantiwar *et al*, 1999)[47]
23	*Bugula neritina* (Bugulidae)	Marine invertebrates	Macrocyclic lactones	Immunomodulator.	(Sredni *et al*, 1990)[48]
24	*Byrsonima crassa* (Malpighiaceae)	Leaves	Flavonoids, tannins, terpenes	Antimicrobial, antioxidant.	(Johnston *et al*, 2009)[49]
25	*Cissampelos pareira* (Menispermiaceae)	Roots	Hayatine alkaloids	Anti-pyretic, analgesic, anti-lithic.	(Bafna and Mishra, 2010)[50]
26	*Cleome gynandra* (Capperdiceae)	Leaf, seeds, rots	Hexacosanol, kaempferol	Anti-inflammatory.	(Gaur *et al*, 2009)[51]
27	*Chlorophytum borivilianum* (Liliaceae)	Roots	Sapogenins	Anti-fungal.	(Thakur *et al*, 2007)[52]
28	*Citrus natsudaidai* (Rutaceae)	Fruits	Auraptene, flavonoids	Anti-oxidant.	(Tanaka *et al*, 1999)[53]
29	*Calendula Officinalis* (Asteraceae)	Flowers	Polysaccharides, carotenoids, flavonoids, triterpenoids	Anti-tumor, anti-viral activity, anti-HIV properties.	(Mani and Lawson, 2006)[54]
30	*Camellia sinensis* (Theaceae)	Leaves	Epigallocatechingallate, quercetin, gallicacid	Anti-cancer activity, hepatoprotective and antioxidant.	(Bhatt *et al*, 2010)[55]
31	*Cannabis sativa* (Cannabaceae)	Leaves	Cannabinoids	Immunomodulatory.	(Killestein *et al*, 2003)[26]
32	*Carpobrotus edulis* (Aizoaceae)	Flowers, fruit	Alkaloids	Immunomodulator.	(Ordway *et al*, 2003)[27]
33	*Centella asiatica* (Umbelliferae)	Herb	Triterpenoidsaponins	Immunomodulator.	(Mali and Hatapakki, 2008)[56]
34	*Cordia superba* *C. rufescens* (Boraginaceae)	Leaf, fruit, bark	Alpha-amyrin	Anti-inflammatory, anti-microbial.	(Costa *et al*, 2008)[57]
35	*Cistanche deserticola* (Orobanchaceae)	Herb	Polysaccharide	Immunomodulator, mitogenic and comitogenic activities.	(Ebringerova *et al*, 2002)[58]

36	*Cliona celata* (Clionaidae)	Sponge	Clionamide, dehydrodopamine	Anti-bacterial activity.	(Sugumaran and Robinson, 2010)[59]
37	*Cordyceps militaris* (Clavicipitaceae)	Fungus	Cordycepin, cordyceps acid	Anti-inflammatory.	(Hsu *et al*, 2008)[60]
38	*Couroupita guianensis* (Lecythidaceae)	Fruits, flowers	Steroids, flavonoids, phenolics	Anti-fungal.	(Pradhan *et al*, 2009)[61]
39	*Crinum latifolium* (Amaryllidaceae)	Herb	Alkaloids	Immunomodulator.	(Zvetkova *et al*, 2001)[62]
40	*Dracocephalum* spp. (Lamiaceae)	Herb	Essential oil	Immunomodulator.	(Amirghofran *et al*, 2000)[63]
41	*Echinacea angustifolia* (Asteraceae)	Flowers	Polysaccharide	Treatment for common cold, immunomodulator.	(Senchina *et al*, 2005)[64]
42	*Eclipta alba* (Asteraceae)	Leaves	Triterpenoidglucoside	Anti-cancer, anti-leprotic, analgesic, anti-oxidant, anti-myotoxic.	(Jayathirtha and Mishra, 2004)[65]
43	*Euphorbia hirta* (Euphorbiaceae)	Herb	Quercitol, myricitrin, gallic acid	Anti-inflammatory activity, sedative and anxiolytic activity.	(SM, 2009)[66]
44	*Evolvulus alsinoides* (Convolvulaceae)	Herb	Alkaloids	Brain tonic.	(Ganju *et al*, 2003)[67]
45	*Ganoderma lucidum* (Polyporaceae)	Whole plant	Flavonoids, triterpenes	Antioxidant.	(Habijanic *et al*, 2001)[68]
46	*Gymnema sylvestre* (Asclepiadaceae)	Leaves	Sapogenins	Antidiabetic, diuretic, antibilious.	(Malik *et al*, 2009)[69]
47	*Haussknechtia elymatica* (Apioideae)	Herb	Phenolics	Immunomodulator.	(Amirghofran *et al*, 2007)[70]
48	*Heracleum persicum* (Apiaceae)	Shurb	Flavonoids, furanocoumarins	Anti-microbial.	(Sharififar *et al*, 2010)[71]
49	*Hibiscus rosasinensis* (Malvaceae)	Flowers	Cyclopropanoids	Anti-diarrheal, anti-inflammatory.	(Gaur *et al*, 2009)[51]
50	*Hyptis suaveolens* (Lamiaceae)	Leaf, flowers	Lupeol, beta-sitosterol	Carminative, anti-spasmodic.	(Jain *et al*, 2005)[72]
51	*Inonotus obliquus* (Hymenochaetaceae)	Mushroom	Polysaccharide	Anti-tumor.	(Caifa Chen *et al*, 2007)[73]
52	*Larrea divaricate* (Zygophyllaceae)	Herb	Lignans	Anti-inflammatory.	(Davicino *et al*, 2007)[74]
53	*Lycium barbarum* (Solanaceae)	Fruits	Polysaccharide-protein complexes	Antioxidant.	(Gan *et al*, 2003)[75]
54	*Lagenaria siceraria* (Cucurbitaceae)	Leaves, fruit	Cucurbitacin, beta-glycosidase	Purgative, emetic.	(Deshpande *et al*, 2008)[76]
55	*Matricaria chamomilla* (Rhabdoviridae)	Flowers	Protein	Immunomodulator.	(De Souza Reis *et al*, 2008)[77]
56	*Mollugo verticillata* (Molluginaceae)	Herb	Quercetin, triterpenoid glycosides	Immunomodulator.	(Ferreira *et al*, 2003)[78]

57	*Morus alba* (Moraceae)	Fruits, leaves, bark	Flavonoids, anthocyanins	Expectorant, hypo-cholesterolaemic, diuretic.	(Bharani *et al*, 2010)[79]
58	*Moringa oleifera* (Moringaceae)	Leaves	Vitamin A, B, C, carotenoids, saponins	Anti-oxidant.	(Gupta *et al*, 2010)[80]
59	*Murraya koenigii* (Rutaceae)	Leaves	Coumarin, carbazole alkaloids, glucoside	Anti-fungal, insecticidal, insecticidal.	(Shah *et al*, 2008)[81]
60	*Nyctanthes arbor-tristis* (Oleaceae)	Leaf, seeds	Iridoidglucosides	Anti-inflammatory, antispasmodic.	(Kannan *et al*, 2007)[82]
61	*Ocimum sanctum* (Labiateae)	Entire plant	Essential oils	Stomachic, anti-spasmodic, anti-asthmatic, hepatoprotective.	(Vaghasiya *et al*, 2010)[83]
62	*Pestalotiopsis leucothes* (Amphisphaeriaceae)	Fungus	Terpenes	Immunomodulator.	(Kumar *et al*, 2005)[84]
63	*Picrorhiza scrophulariiflora* (Scrophulariaceae)	Roots	Iridoid glycosides, amphicoside	Anti-oxidant.	(Smit, 2001)[85]
64	*Panax ginseng* (Araliaceae)	Fruits, root	Saponins (ginsenosides, panaxdiol, panaxtriole and oleanolic acid)	Adaptogenic properties, anti-arrhythmic.	(Panax Ginseng. Monograph, 2009)[86]
65	*Piper longum* (Piperaceae)	Fruits	Alkaloids	Antioxidant.	(Sunila and Kuttan, 2004)[87]
66	*Rhodiola imbricate* (Crassulaceae)	Rhizomes	Phenolics	Immunostimulating properties.	(Mishra *et al*, 2008)[88]
67	*Randia dumetorum* (Rubiaceae)	Fruits	Saponins, triterpenes	Chlorosis, anti-arthritic.	(Satpute *et al*, 2009)[89]
68	*Silybum marianum* (Asteraceae)	Flowers	Flavonoid	Anti-oxidant.	(Meeran *et al*, 2006)[90]
69	*Salicornia herbacea* (Chenopodiaceae)	Herb	Polysaccharides	Immunomodulator.	(Im *et al*, 2006)[91]
70	*Terminalia arjuna* (Combretaceae)	Leaves, bark	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, prescribed for hypertension.	(Halder *et al*, 2009)[92]
71	*Thuja occidentalis* (Arborvitae)	Leaves	Polysaccharides	Immunomodulator.	(Gohla *et al*, 1992)[93]
72	*Tinospora cordifolia* Miers. (Menispermiaceae)	Entire herb	Alkaloidal constituents	Hypoglycaemic agent, anti-pyretic.	(Kirti *et al*, 2004)[94]
73	*Urena lobate* (Malvaceae)	Roots, flowers	Flavanoids	Diuretic, emollient, anti-spasmodic.	(Rinku *et al*, 2009)[95]
74	*Viscum album* (Loranthaceae)	Leaves and young twigs, berries	Viscotoxins, polyphenols, polysaccharides	Anti-tumor effect.	(Elluru *et al*, 2007)[96]

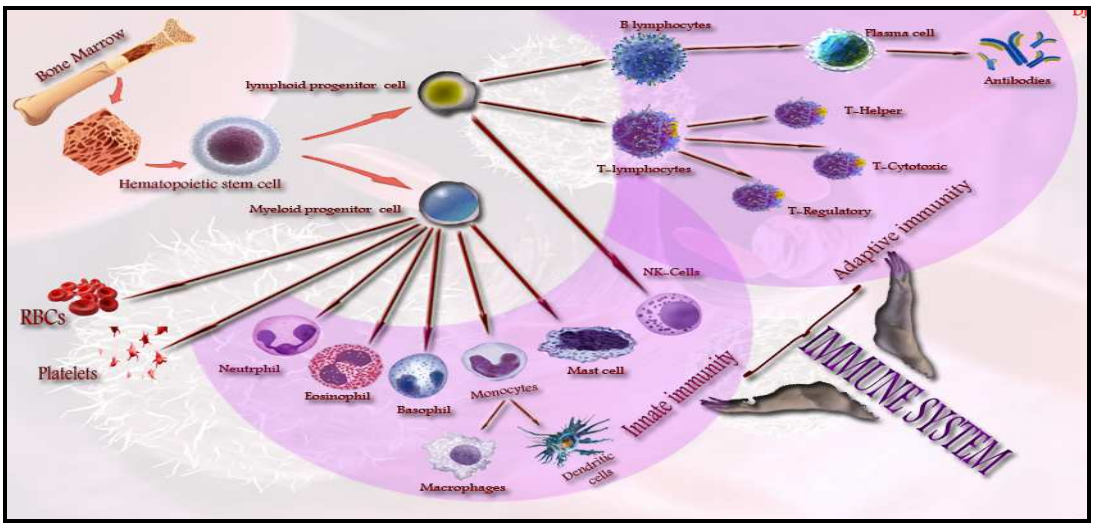


Figure No.1: Origin and types of immune system cells (Created by Our own Team)

Figure No.2: General aim of the study (Created by Our own Team)

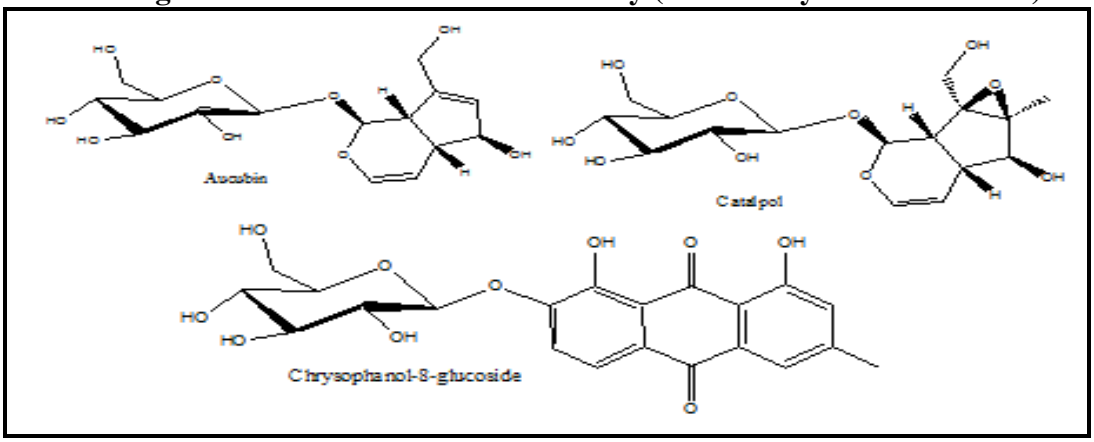


Figure No.3: Structure of aucubin and catalpol, two of the most common iridoids in the plant kingdom and chrysophanol-8-glucoside an immunomodulators anthraquinone glycosides

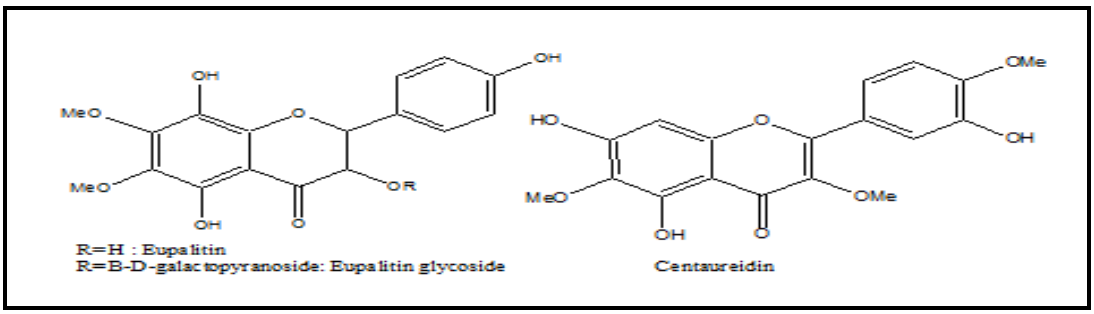


Figure No.4: Structure of eupalitin and centaureidin, flavonoids showing immunomodulatory activity

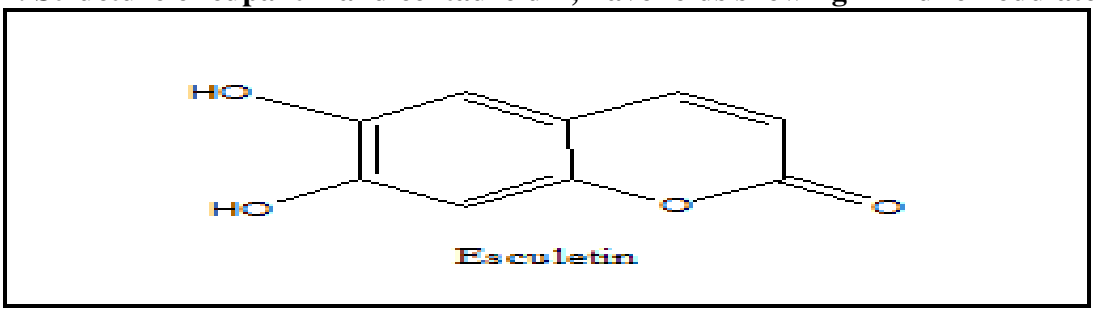


Figure No.5: Structure of immunomodulatory coumarin (Esculetin)

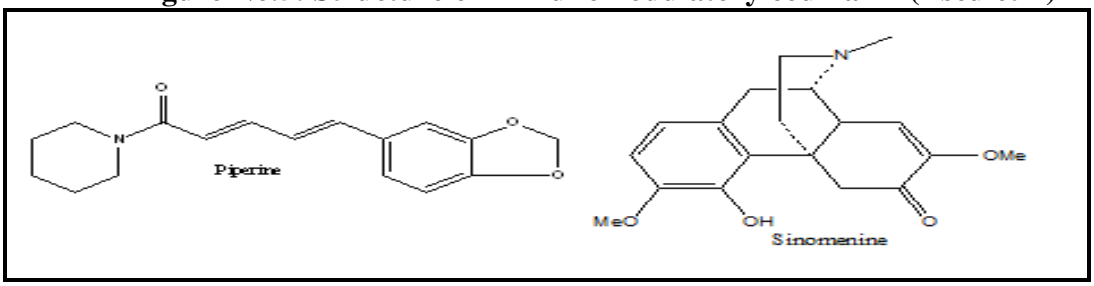


Figure No.6: Structure of some plant alkaloids with immunomodulatory activity Thiosulfinates

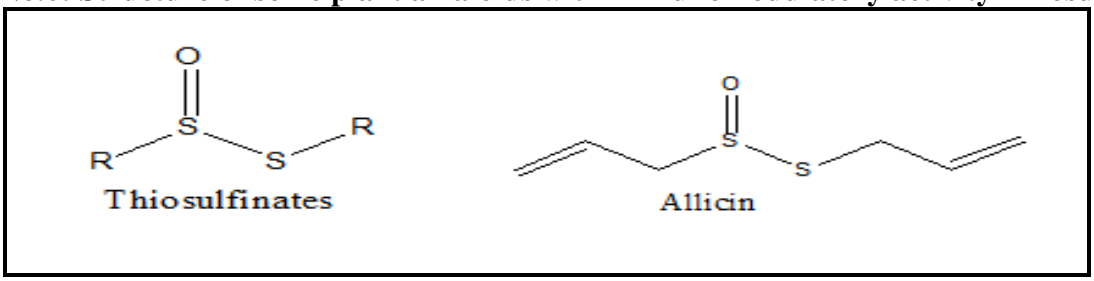


Figure No.7: Structure of Allicinthiosulfinate derived from garlic which has immunomodulatory activity

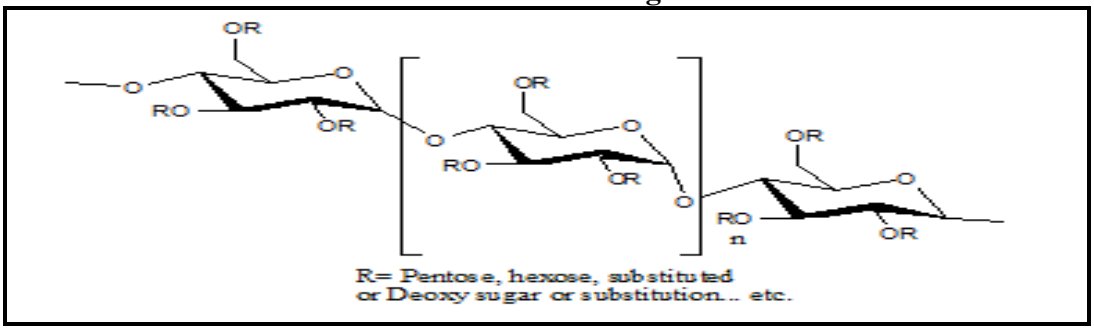


Figure No.8: Structure of main building unit of polysaccharides

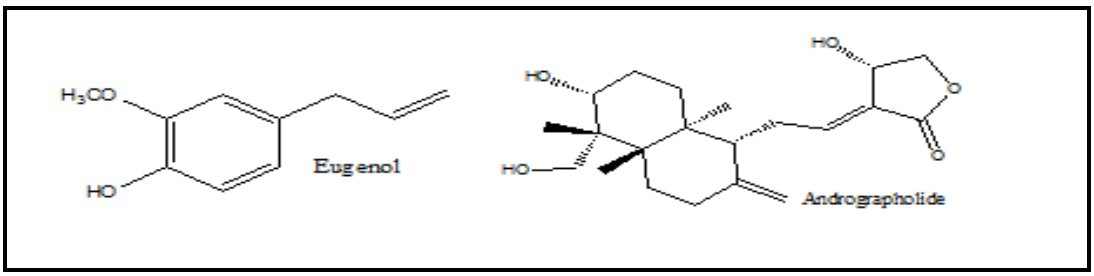


Figure No.9: Structure of eugenol and andrographolide which have immunomodulatory activities

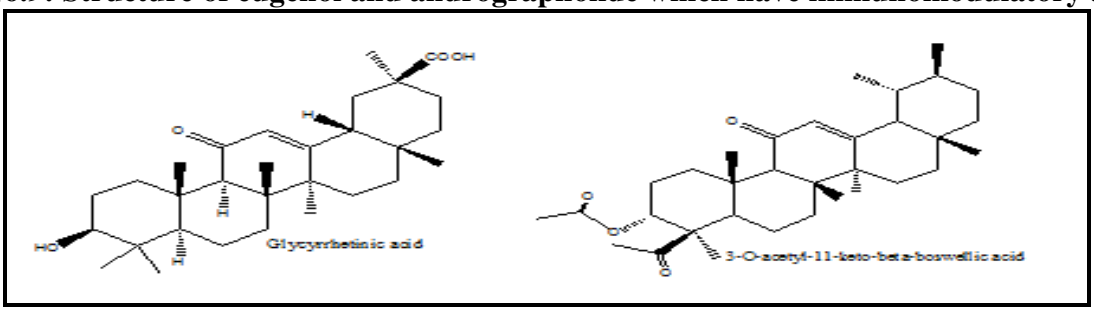


Figure No.10: Structure of glycyrrhetinic acid and boswellic acid "AKBA", triterpene acids isolated from *Glycyrrhiza glabra* and *Boswellia* spp

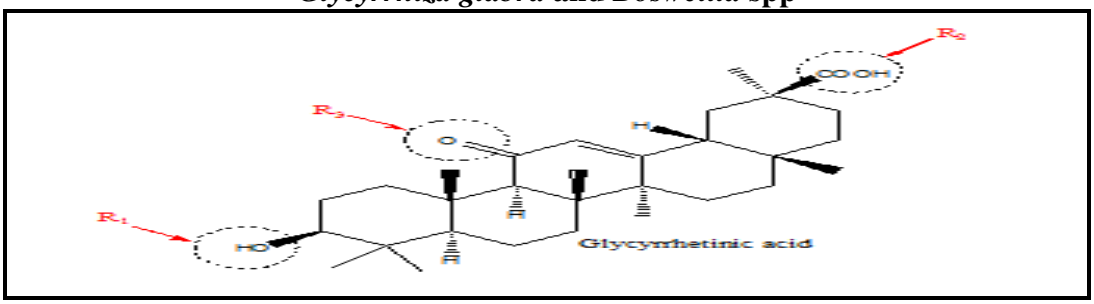
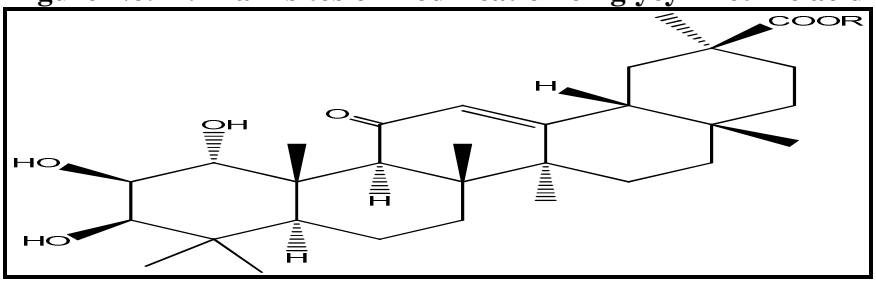
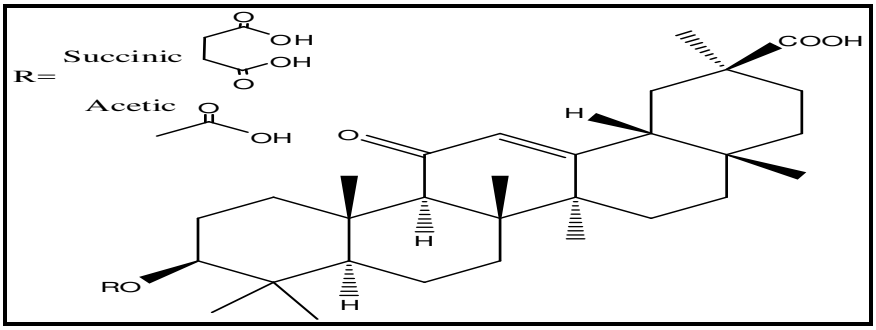
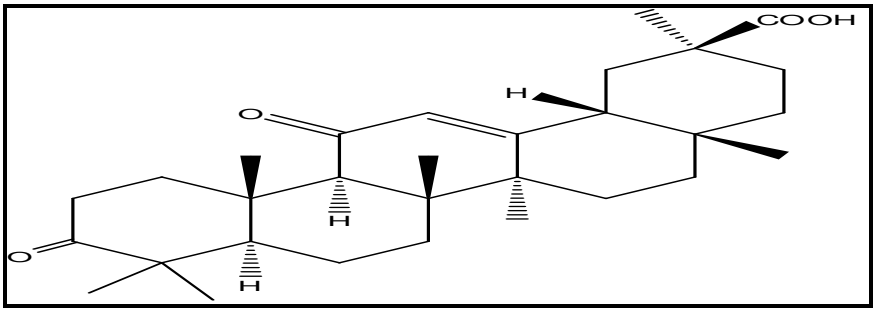
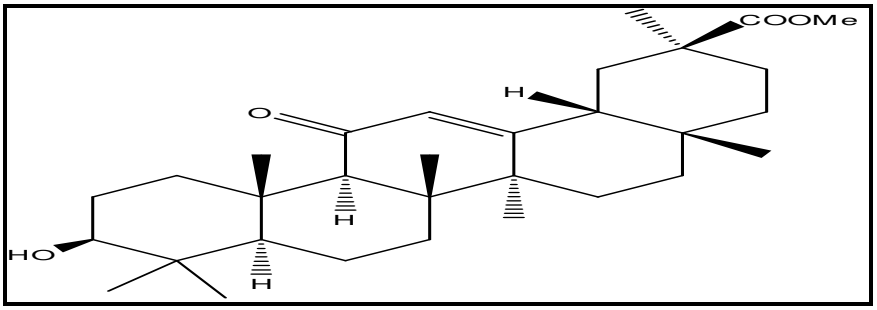


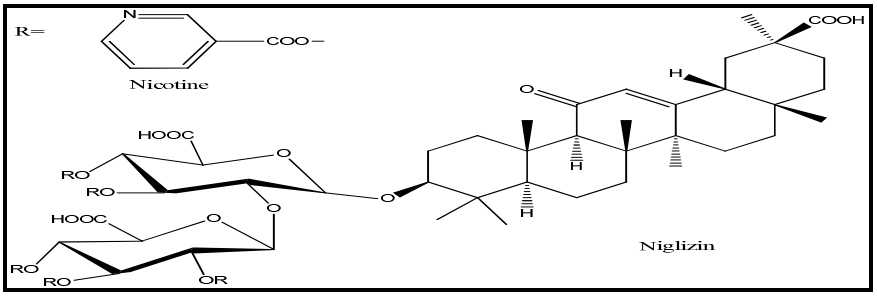
Figure No.11: Main sites of modification on glycyrrhetinic acid

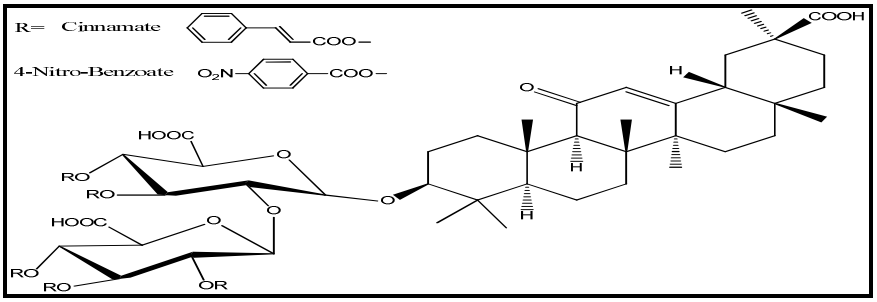


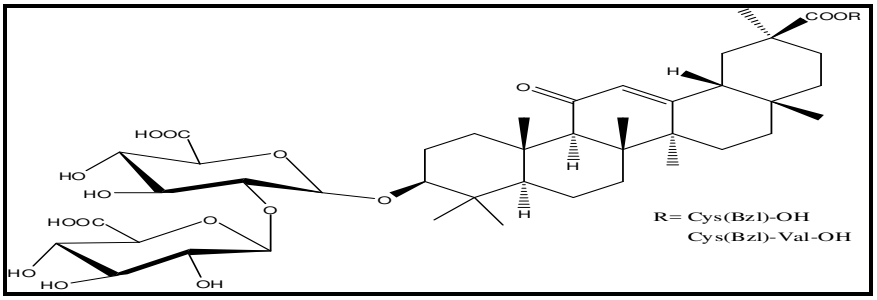


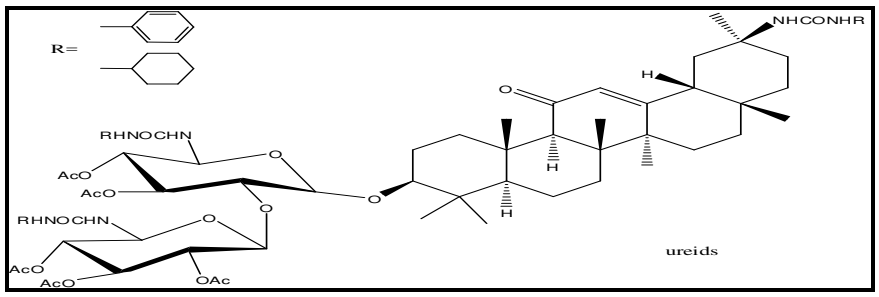

COOH
H
O
H
O
H

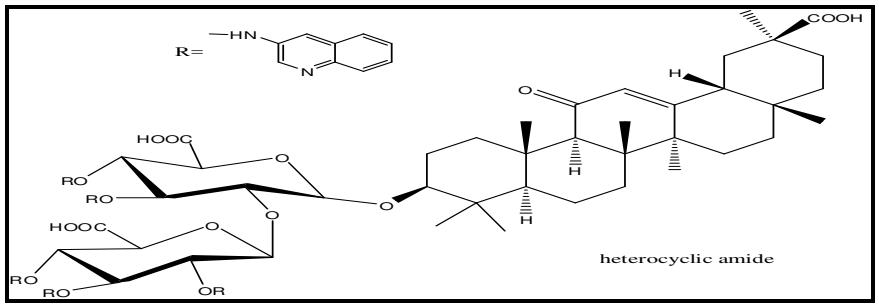

COOMe
H
O
H
HO
H

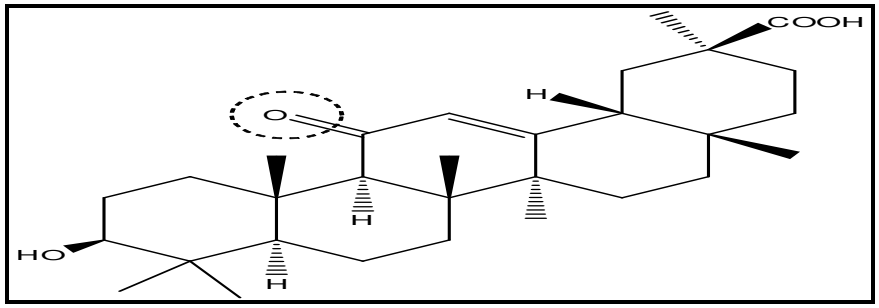

R=
N
COO–
Nicotine
COOH
H
O
HOOC
O
RO
RO
O
HOOC
O
RO
RO
OR
H
O
H
Niglizin

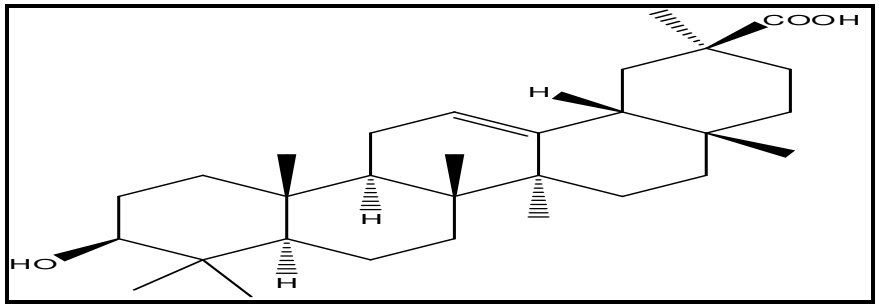

R= Cinnamate
COO–
4-Nitro-Benzoate
O2N
COO–
COOH
H
O
HOOC
O
RO
RO
O
HOOC
O
RO
RO
OR
H
O
H

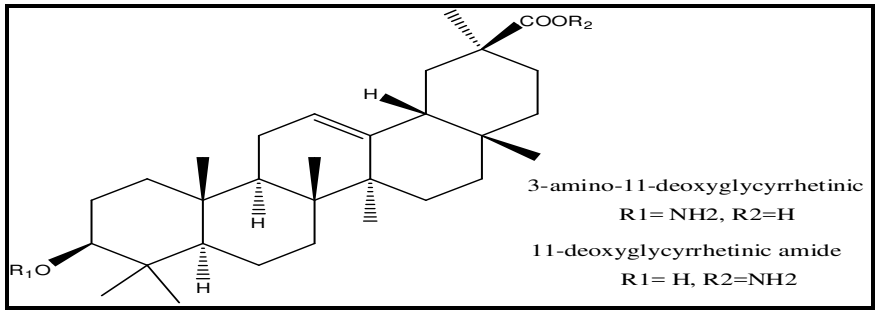

COOR
H
O
HOOC
O
HO
HO
O
HOOC
O
HO
HO
OH
H
O
H
R= Cys(Bzl)-OH
Cys(Bzl)-Val-OH


R=
NHCONHR
RHNOCHN
AcO
AcO
RHNOCHN
AcO
AcO
OAc
ureids


R=
HN
N
COOH
HOOC
RO
RO
HOOC
RO
RO
OR
heterocyclic amide


COOH
HO


COOH
HO


COOR2
R1O
3-amino-11-deoxyglycyrrhetinic
R1= NH2, R2=H
11-deoxyglycyrrhetinic amide
R1= H, R2=NH2

CONCLUSION

Immunomodulation either using natural products or their semisynthetic derivatives can provide support to achieve the healthy state in normal or diseased patients. Also, agents that can affect immunity in a situation of immune impairment can then be used as co-therapy with chemotherapy (Wagner *et al*, 2012)[113]. Bone marrow is a sensitive target especially to cytotoxic agents due to high degree of cell proliferation. In fact, under immunosuppression therapy, bone marrow is the most affected organ which in turn results in leucopenia and thrombocytopenia (Bafna and Mishra, 2006)[114]. Triterpenoidal and steroidal saponins (Yesilada *et al*, 2005)[115] are proven to have versatile pharmacological activities, such as being anti-hepatotoxic, molluscicidal, antifungal, cytotoxic, antiviral and immunomodulator.

Immunomodulation activities of terpenoids such as glycyrrhizin, ursolic acid and oleanolic acid, have been reported (Raphael and Kuttan, 2003)[116]. Many medicinal plants can exert immunomodulatory activity in experimental models at a specific dose. Different types of *in vivo* and *in vitro* screening models both have been employed to study that activity. Some medicinal plant extracts can produce immunostimulation (e.g., *Glycyrrhiza glabra*, *Ocimum sanctum*), and others can produce immunosuppression (*Alternanthera tenella*). Finally, various phytochemical active isolates (e.g., glycosides, terpenoids, saponins, steroids, alkaloids, coumarins, and flavonoids) may exhibit a wide range of immunomodulatory activities.

Immunity is the body ability to identify and resist harmful pathogen. The immune system has a multilayered construction, with several stages of defenses. The skin is the first barrier of immunity.

In recent years, there is an upsurge in the clinical use of natural products or their derivatives due to being free from serious toxic effects and better efficacy. Additionally, steady increase in the resistant microorganism strains to antibiotics and serious averse manifestations brought about by the synthetic drugs has incited researchers to search for natural immunomodulators to fight different infections (Shukla *et al*, 2014)[117].

Mechanisms of action of an immunomodulator goes mainly through stimulation of phagocytosis, activation of macrophages, stimulation of lymphoid cells, enhancement of nonspecific cellular immune function, increasing natural killer cell numbers and nonspecific mediators of immune system, increasing the production of antigen-specific antibodies, counter the effect on leukopenia induced by chemotherapy, and increasing total counts of circulating white blood cells and induction of variety of cytokine levels.

ACKNOWLEDGEMENT

I would like to thank my student Mr. Diaaeldin M. Elimam, and my colleagues, Drs. Hosam M. Zaghloul, Fatma M. Abdel Bar, for their valuable contribution and support during the practical part of this study. Also, I would like to thank FAB-Lab, Liver Research Lab, and those who maintain it.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Farid A. Badria. Natural products and medicinal plants: Boosting Immune System against COVID-19 and other viruses, *International Journal of Research in Pharmaceutical and Nano Sciences,* 9(2), 2020, 46-71.