Medicinal plants of antimicrobial and immunomodulating properties

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Constituents of plant, alongside other characteristic items, are regularly to a great degree helpful as "lead" mixes for the outlining of manufactured analogs with either enhanced remedial movement or decreased toxicity. In recent years, due to development of microbial pathogens emergence of new multi-drug resistance pathogens, the antibiotics are now in danger of losing their efficacy. Many plants can eradicate human pathogens without toxic side effects and environmental hazards, compared to synthetic antibiotics.

On the other side, the immune system is a remarkably sophisticated defense system protects animals from invading microorganisms. However, at specific circumstances the immune system be controlled, managed and incidentally should be stifled. Incitement of the insusceptible reaction is exceedingly alluring in specific cases, for example, immunocompromised people. While, the suppression of is imperative in transplant beneficiary, and hypersensitive and patients with inflammation.

Interestingly, many medicinal plants are claimed not only as potential antimicrobials but also as immunomodulators. This dual action feature is important and requisite in combat against antibiotics-resistant pathogens. This review highlights the exploration of the variant mode of actions of medicinal as a new approach of phytotherapy against the prevalent multi-drug resistant pathogens.

Keywords: antimicrobial; antibacterial; antifungal; immunomodulating, phytotherapy

1. Introduction

No doubt that, man appeared on Earth teeming with macro and microorganisms. As man striving to survive in life, he started innovate numerous methods to get rid annoying macro-organisms from tiny insects to massive animals. Despite the assumption that Robert Hooke and Antoni van Leeeuwenhoek discovered the microorganisms in the sixteenth century [1]; actually, man discovered dealing with microbes since times immemorial; he used microbes to ferment milk and fruits, preserve food with drying, salting, sweating, and eventually curing microbial diseases by means of some natural products.

Some fossil records tells the true story, fossil evidences showed that a Neanderthals human lived since 60 000 years ago in Mesopotamia (Iraq), had used a medicinal plant named *Alcea rosea* and this plant is still used in traditional medicine today [2]. Logically, ancient human must observed that decaying corpses attributed to some invisible creatures, now we call it microorganisms!

In fact, our planet is truly the planet of microbes, there were the first creatures arisen on Earth 3.8 to 3.9 billion years ago, paved the environment of earth for all subsequent living forms [3]. These smart microbes are able to survive in almost all environmental conditions, even some bacteria looks extremely perennial, viable specimens of ancient bacteria have been revived from 40-million-year-old amber and from 250-million-year-old salt crystal [4]. Accordingly, we-the human- should understand the lesson, it is impossible to eradicate pathogenic microbes with our limited synthetic drugs such as antibiotics, but we can put them under control by means of integrated efforts of environmental, pharmacological, microbiological, immunological and economical sciences.

The role of plants in medicine dates back to immemorial times, individuals remain utilizing the natural prescription for the treatment of different sorts of sicknesses [5,6]. Up today, ethnomedicine still assume the hub part in the inquiry and advancement of new medications [7]. One fourth of every single restorative remedy depend on substances got from plants or plant-determined engineered analogs and 80% of world's populaces - basically those in creating nations - depend on plant-inferred prescriptions for their human services. Additionally no less than twelve intense medications have been gotten from blossoming plants amid the period 1950 – and 1990 [8].

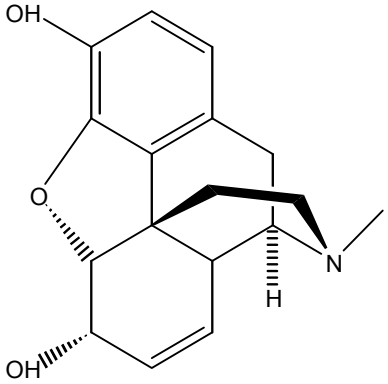
2. Medicinal plants and drug discovery

Plants are a profitable wellspring of new regular items. In spite of the accessibility of various methodologies for the discovery of therapeuticals, natural products still stay as one of the best repositories of new auxiliary sort [9]. It has been

assessed by the World Health Organization (WHO) that approximately 80% of the world's population relay mainly on traditional medicine for their primary health care [10,11]. Plants likewise assume an imperative part in the care frameworks of the staying 20% of the population, chiefly living in developed countries [12]. Examination of information on solutions apportioned from group drug stores in United States from 1959 – 1980 demonstrated that around 25% contained plant extracts or active principles derived from higher plants. Currently, at least 119 chemical substances, derived from 90 plant species, can be considered as important drugs that are in use in one or more countries. Of these 119 drugs, 74% were discovered as the results of chemical studies directed at the isolation of the active substances from plants used in traditional medicine [12]. Table 1 showing some modern drugs derived from nature. Later, on a survey was carried out during the period (1993 - 1997). Grifo et al., [13] shown that, the natural products still assume a noteworthy part in medication treatment, as more than half of the most-recommended medications in the US had a natural products either as the medication, or as an "ancestor" in the synthesis or plan of the specialist.

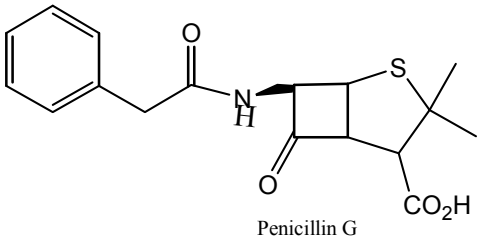
The possibility of "pure" compounds as drugs may be traced to the isolation of the active principles of commonly used plants. The German chemist, Karl Wilhelm Scheele (1724 – 1786 AD) extracted some simple compounds like glycerol, oxalic acid, lactic acid, tartaric acid and citric acid from various organic sources including vegetables and animals [12]. The discovery for useful drugs from the plant kingdom of known structures, however, did not really begin until about 1806 AD, when morphine was separated from the dried latex of Papaver somniferum (opium) by F. W. Sertürner. These isolation studies can be considered the leading chance for generationof the first commercial pure natural product, morphine, by E. Merck in 1826, while, the first semi-synthetic pure drug based on a natural product aspirin by Bayer in 1899 [14].

The brilliant time of anti-microbials started with the fortunate revelation of penicillin by Alexander Fleming in 1928 and revealed in the British Medical Literature in 1929 [14].

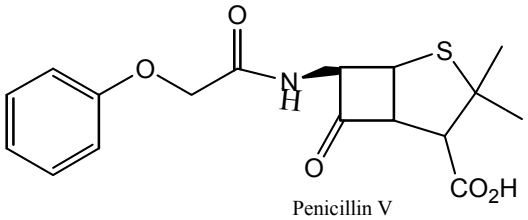


Morphine

The golden age of antibiotics began with the serendipitous discovery of penicillin by Alexander Fleming in 1928 and reported in the British Medical Literature in 1929 [14].

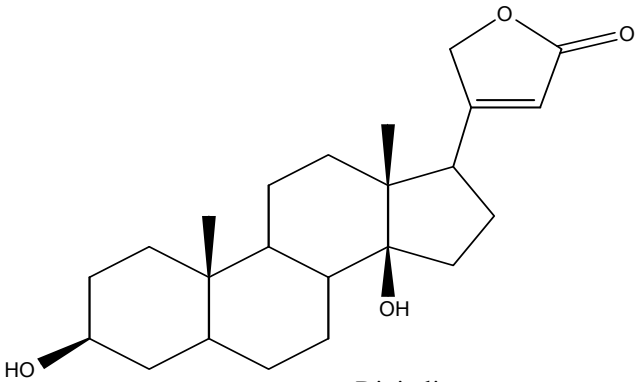


Penicillin G



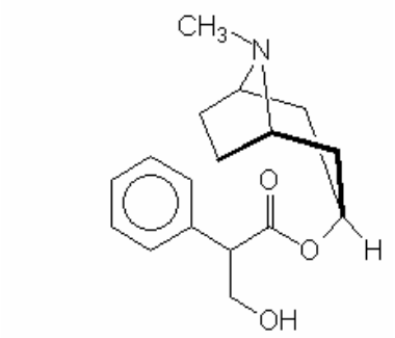
Penicillin V

Foxglove (Digitalis purpurea), a local of Western Europe, is the wellspring of the essential medication digitalis (confined before over one century), tremendously utilized as a part of the medication of cardiac issue (cardiotonic). The active principle, digitalin, slows and regulates the heartbeat, making the contractions more effective and improving the tone and rhythm [14].



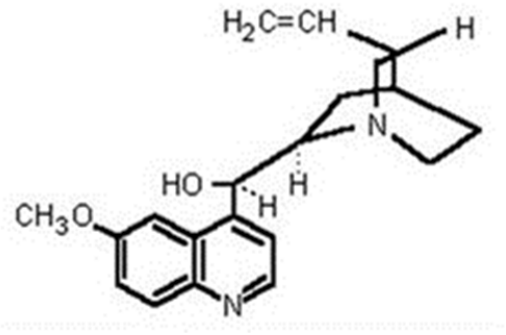
Digitalis

Atropine is an alkaloid isolated from Atropa belladonna, Datura stramonium and other Solanaceae in 1850 AC. And known as mydriatic, antispasmodic and cycloplegic agent and smooth muscle relaxant



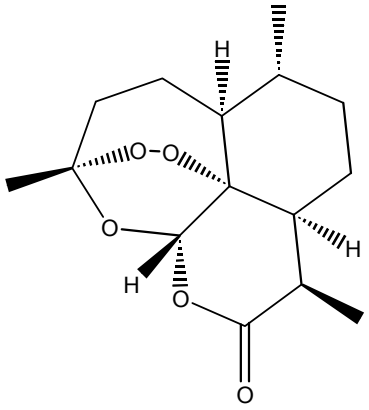
Atropine

Qunine is alkaloid from Cinchona officinalis and most other Cinchona spp., traditional antimalarial drug since 1640 AD especially important in treating Plasmodium falciparum infection which is resistant to other antimalarial drugs. It was isolated in 1820 AD and introduced as drug in 1825 [14].



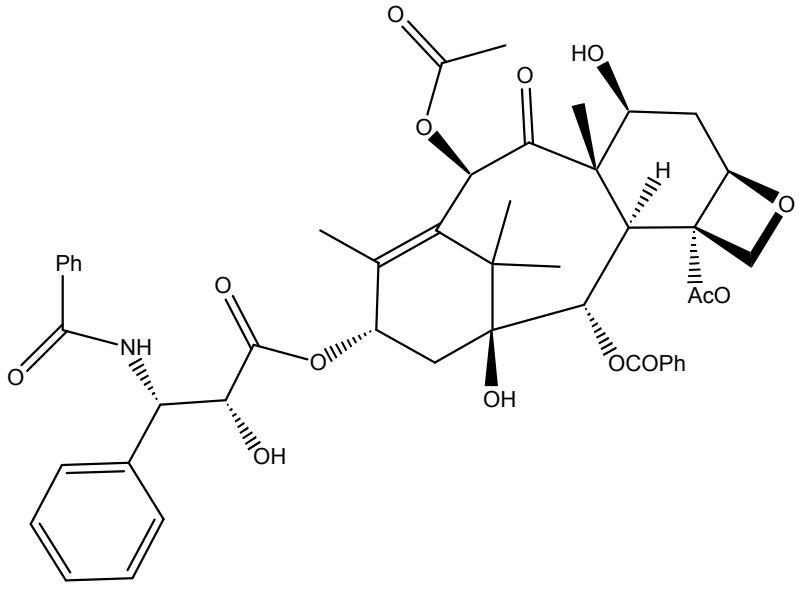
Quinine

The inspection of data from Chinese herbal remedies promoted to the investigation of extracts of Artemisia annua (worm wood) which is utilized since hundreds of years as an antimalarial medication the active agent was isolated and identified as sesquiterpene endoperoxide, named artemisinin in 1972 [14].



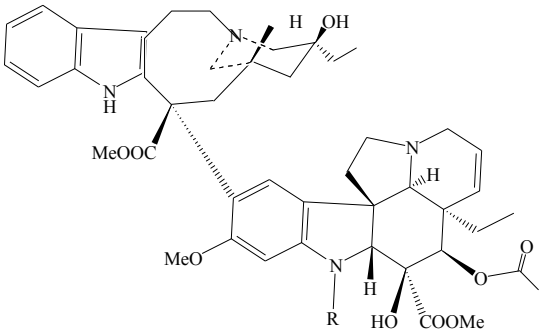
Artemisinin

The complex diterpenes Taxol® (Paclitaxel) was first isolated from the bark of Taxus brebifolia, which historically was used by several American native tribes for the treatment of some non cancerous conditions [14].



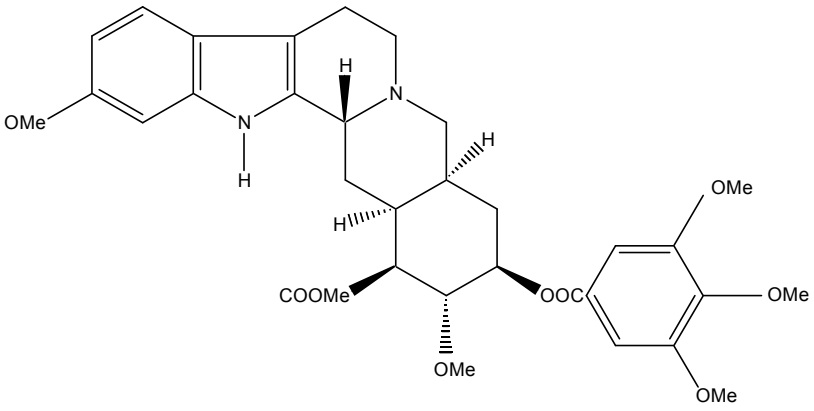
Taxol® (Paclitaxel)

The introduction of anticancer drugs such as the Vinca alkaloids vinblastine (Velbe®) and vincristine (Oncovin®), isolated from Catharanthus roseus, has brought cutting edge marvels. They are antimitotic agents and used in combination with other agents for the treatment of a wide assortment of cancers [14].



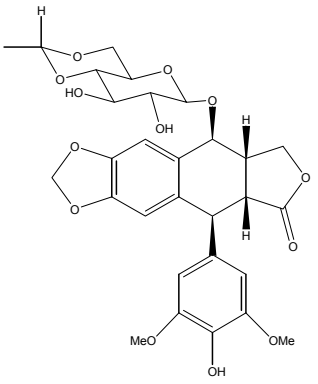
R = CHO vincristine
R = CH_3 vinblastine

Reserpine, an alkaloid isolated from Rauwolfia serpentina, and other Rauwolfia spp., is characterized by broad spectrum pharmacological activities such as antiadrenergic, anticonvulsant and antineoplastic agents. It possesses sedative tranquilliser properties and acts as antihypertensive agent by depleting stores of noradrenaline in sympathetic neurones. Many semisynthetic analogues have been investigated [14].

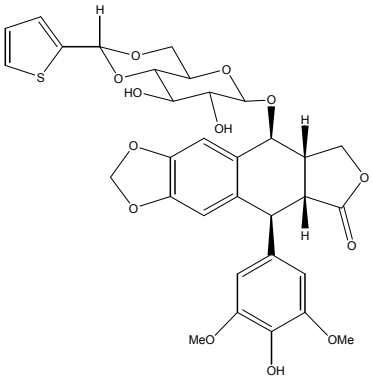


Reserpine

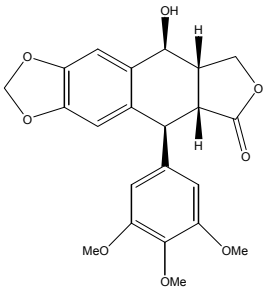
The precursor of two clinically active ingredients, etoposide and teniposide, is epipodophyllotoxin, which is a naturally occurring primer of podophyllotoxin. It was separated as active antitumor ingredient from different species of the genus Podophyllum roots. These plants have a long history of therapeutic uses by early local American and Asian cultures [14].



Etoposide



Teniposide



Podophyllotoxin

Notwithstanding the previously mentioned, substantial quantities of medications from restorative plants were discovered and presented in current pharmaceutical amid the last two centuries.

Table (1) Some modern drugs derived from nature

Year of production	Drug	Commercialized as	Indication	Company
1826	Morphine	Normal compound (p)	Analgesic	Merck
1899	Acetylsalicylic acid (aspirin)	Synthetic analogue	Analgesic, antiphogistic, etc.	Bayer
1941	Penicillin	Normal compound (m)	Antibacterial	Merck
1964	Cephalothin	Semi-synthetic derivative (m)	Antibacterial	Eli Lilly
1983	Cyclosporine A	Normal compound (m)	Immunosuppressant	Sandoz
1987	Artemisinin	Normal compound (p)	Antimalarial	Baiyunshan
1987	Lovastatin	Normal compound (m)	Antihyperlipidemic	Merck
1989	Simvastatin	Semi-synthetic derivative (m)	Antihyperlipidemic	Merck
1989	Pravastatin	Semi-synthetic derivative (m)	Antihyperlipidemic	Synko
1990	Asarbose	Normal compound (m)	Antidiabetic (type II)	Bayer
1993	Paclitaxel (Taxol)	Normal compound (p)	Anticancer	BMS
1993	FK 506 (Tacrolimus)	Normal compound (m)	Immunosuppressant	Fujisawa
1994	Fluvastatin	Synthetic analogue (m)	Antihyperlipidemic	Sandoz
1995	Docetaxel (Taxotere)	Semi-synthetic derivative (p)	Anticancer	Rhone-PR
1996	Topotecan (Irinotecan)	Semi-sythetic derivative (p)	Anticancer	SKB
1996	Miglitol	Synthetic analogue (m,p)	Antidiabetic (type II)	Bayer

m = microbial metabolite, p = plant metabolite
BMS = Bristol-Meyers Squibb, Rhone-PR = Rhone-Poulenc Rorer, SKB = Smith Kline Beecham.
* Source: Grabley, S. and Thiericke, R. [15].

3. Trip from discovery to development

It includes all processes from identifying drug candidate (new pharmaceutical drug) up to the market, after identification of compound either from nature or synthetic passes through the process of drug discovery. Then it continues to pre-clinical research on microorganisms and animals, filing for regulatory status, such as the United States Food and Drug Administration (FDA) for an investigational new drug to initiate clinical trials on humans, and it may include the step of obtaining regulatory approval with a new drug application to market the drug.

Commonly, scientists find new medications through:

New bits of knowledge into a sickness procedure that permit scientists to outline an item to stop or invert the impacts of the infection. Many trial of atomic mixes to discover conceivable advantageous impacts against any of countless existing medications.

New advancements, for example, those that give better approaches to target medicinal items to particular destinations inside the body or to control hereditary material. At this phase simultaneously, a huge number of mixes might be potential

possibility for advancement as a restorative treatment. After early testing, in any case, just few mixes search promising and call for further review that have unexpected impacts.

4. Plants of Antimicrobial and immunomodulating effects

In this era, the world witnesses a dramatic increase in drug resistance to modern medicine in microbial pathogens [16].

Worldwide, the reasons behind emerging and re-emerging of new infections are multi-factorial. However, it could be attributed to three major factors:

1-The microbes which are able to adapt and acquire new virulent factors;
2-The human activities and socio-economical factors; and
3-The climatic changes. [17].

Accordingly, the human needs to be well prepared to face these emerging infections. Numerous plants were reported to have dual effects, antimicrobial and immunomodulating activity (Table 2). These plants are recommended for further investigations in order to discover new alternative drugs.

5. Future prospective

Interest in medicinal plants has greatly increased due to the dramatic collapse of modern synthetic medicine, particularly the antimicrobial and immune-modulating drugs. Thus, it is expected to witness a dramatic shift from synthetic medicines to herbal medicines; hence, pharmaceutical companies should change their strategies and return to nature. It is well known that these pharmaceutical companies are governed by financial standards rather than humanitarian standards, so the governments all over the globe, scientific community and institutions should increase the financial support, funds and investments in medicinal plants and natural products research. Undoubtedly, with up to 80% of population in developing countries and growing demand on herbal remedies in developed countries, the world in near future may shift to phytotherapy and introduce plant derived compounds in modern medicine.

Table 2. Plants of dual effects; immunomodulating and antimicrobial activities and/or their isolated compounds

Plant	Activity	References
Eupatorium arnottianum	The dichloroethane extract inhibited the complement hemolytic activity on both classical and alternative complement pathways (CP and AP respectively) with IC50 5.0 ± 0.1 and 101.3 ± 1.5 µg/ ml respectively	[18]
	The aqueous extract as reported to have antibacterial activity against some gram positive bacteria and the methanol extract was found to have antifungal effects against filamentous fungi	[19]
Phyllanthus sellowianus	The aqueous extract inhibited the complement hemolytic activity on both classical and alternative complement pathways (CP and AP respectively) with IC50 22.0 ± 2.2 280.6 ± 7.1 µg/ ml respectively	[18]
	Phyllanthus sellowianu is *now* thought of as a *variety of phyllanthus niruri, the latter showed that* the methanolic extract contains effective antibacterial agent to treat bacterial infections (Gram-positive and Gram-negative bacteria), the antimicrobial potency of the extract was comparable with that of the standard antibiotic chloramphenicol.	[20]
Aronia melanocarpa	Polyphenols isolated from *A. melanocarpa* possess immune modulating activity Cyanidin, procyanidin B2, B5 and C1 and proanthocyanidin-rich fractions were highly active in the complement-fixing assay. In addition, the oligomeric procyanidins displayed dose-dependent inhibitory effects on LPS-induced NO production in murine RAW 264.7 macrophages.	[21]
	The fruit extract of *Aronia melanocarpa* exhibited antibacterial activity against Gram-positive bacteria (Bacillus cereus and Staphylococcus aureus) and -negative bacterium Pseudomonas aeruginosa, but did not have influence on Escherichia coli. Also, it did not show antifungal activity.	[22]
Glinus oppositifolius	An immunomodulating pectic polymer, GOA1, obtained from the aerial parts of the Malian medicinal plant Glinus oppositifolius (L.) induces proliferation of B cells and the secretion of IL-1b by macrophages, in addition to a marked increase of mRNA for IFN-c in NK-cells. To elucidate structure–activity relations the native polymer and the digested fractions were tested for complement fixing activity and intestinal immune stimulating activity. The acid hydrolysed fraction showed reduced complement fixing activity.	[23]
	The leaf extracts of Glinus oppositifolius exhibited antibacterial activities against the non-resistant and multidrug-resistant strains of Gram-negative bacteria *Escherichia coli, Pseudomonas. aeruginosa* and *Acinitobacter baumanii*.	[24]
Picrorhiza kurroa	*The ethanolic extract of Picrorhiza kurroa was* found to be a potent immunostimulant, stimulating both cell-mediated and humoral immunity.	[25]
	The methanolic and aqueous extracts of *Picrorhiza kurroa* showed potent effect against numerous pathogenic bacterial and fungal strains; *Pseudomonas aeruginosa*, *Staphylococcus aureus, Bacillus subtilis, Micrococcus luteus*, *Escherichia coli* and *Candida albicans*, *Aspergillus niger*, respectively. Moreover, the significant antimicrobial activity was shown by methanolic extract only, against *P. aeruginosa* and *S. aureus;* while moderate activity against *E. coli, B. subtilis* and *M. luteus.*	[26]
Tylophora indica	The ethanolic extract appeared to stimulate phagocytic function while inhibiting the humoral component of the immune system.	[25]
	The crude leaf extracts of *Tylophora indica* revealed considerable antibacterial activity against *Basillus subtilis*, *Staphylococcus aureus*, *Mycrococcus luteus* and *Pseudomonas aergenosa*. While, *Escherichia coli showed no sensitivity*. In addition, pure compounds of *Tylophora indica* displayed significant antibacterial activity at lower concentrations against all tested bacterial strains (except *E. coli*) and good antifungal activity against against *Aspergillus niger, Aspergillus fumigatus* and *Trichoderma viridae*.	[27]

Aconitum heterophyllum	The ethanolic extract appeared to stimulate phagocytic function while inhibiting the humoral component of the immune system The methanolic extract of *Aconitum Heterophyllum* showed significant inhibition of the growth of Gram positive bacteria; *Staphylococcus aureus* and *Bacillus subtilis*. And Antifungal activity against *Candida albicans* and *Aspergillus flavus*.	[25] [28]
Holarrhena antidysenterica	The ethanolic extract appeared to stimulate phagocytic function while inhibiting the humoral component of the immune systeme The alkaloids extracted from seeds have antibacterial and antidiarrhoeal agents. Leaves and bark exhibited antibacterial activity against *Staphylococcus. aureus and Bacillus Cereus* followed by *Escherichia coli, Listeria. monocytogenes, Pseudomonas aeruginosa* and *Yersinia pestis.*	[25] [29] [30]
Tinospora cordifolia	The ethanolic extract appeared to improve the phagocytic function without affecting the humoral or cell-mediated immune system. The ethanol extract has significant antibacterial activity against Escherichia coli, Proteus vulgaris, Enterobacter faecalis, Salmonella typhi, Staphylococcus aureus and Serratia marcesenses	[25] [31]
Ocimum gmtissimum	The ethanolic extract appeared to improve the phagocytic function without affecting the humoral or cell-mediated immune system. The leaves possess antibacterial and antifungal agents.	[25] [32]
Hemidesmus indicus	The ethanolic extract suppressed both the cell-mediated and humoral components of the immune system. Aqueous extracts from roots revealed significant antibacterial activity against some pathogenic bacteria.	[25] [33]
Anemarrhena asphodeloides	A potent modulating activity was observed in a crude polysaccharide fraction (AS-1) from the rhizome of Anemarrhena asphodeloides Bunge. Oral administration of AS-1 (100 mg/kg/ day) to aged BALB/c mice enhanced productions of IL-10, IFN-c and IL-6 from Peyer's patch immunocompetent cells, and its oral administration to ovalbumin (OVA)-fed B10.A mice led to significant suppression on induction of OVA-specific IgE in systemic immune system. Further fractionation of the polysaccharides in the crude polysaccharide fraction, AS-1, yielded 4 polysaccharide fractions that were potently active, and contained glucomannans. Treatment of these polysaccharide fractions with endo-b-D-(1?4)-mannanase significantly decreased their activities. This plant claimed having antimicrobial activity, although data regarding the antimicrobial activity are scanty.	[34] [35]
Coffea arabica	Immunological tests showed that AGP (arabinogalactan-protein isolated from instant coffee powder of Coffea arabica beans) affected some mediators of immunocompetent cells of immune system as TNF-alfa, IFN-gamma and IL-2 cytokines. It seems that coffee AGP is a good inductor of both pro-inflammatory cytokines TNF-alfa and IFN- gamma, however, less potent in TNF-alfa induction in comparison with that of beta-d-glucan. It showed Bactericidal activity against different human pathogenic bacteria.	[36] [37]
Parkia biglobosa	Polysaccharides were extracted from the bark of Parkia biglobosa with 50% ethanol–water, 50 ◦C and 100 ◦C water, and seven active fractions obtained by anion exchange chromatography and gel filtration. The acidic fractions PBEII-I and PBEII-IV were the most active in the complement fixation assay, but the other fractions were also potent compared to the positive control BPII from Biophytum petersianum. Fractions PBEII-I and PBEII-IV were also the most potent fractions in stimulating macrophages to release nitric oxide. The ethanolic extracts of leaves and roots showed inhibitory activity against Escherichia coli, Proteus mirabilis, Pseudomonas sp., Klebsiella sp.,Staphylococcus sp., Streptococcus aureus, and Bacillus sp., respectively.	[38] [39]

Acacia nilotica	Fruits and barks of Acacia nilotica ethanolic extracts possess average inhibitory effects in the range of 70.7, 67.1, % on both types of phagocytes (PMNs and MNCs), respectively, at a 6.25 µg/mL concentration. The methanol extract of the pods of Acacia nilotica exhibited antibacterial potential against all tested bacteria, particularly the Gram-negatives.	[40] [41]
Khaya senegalensis	Leaves and barks of Khaya senegalensis ethanolic extracts possess average inhibitory effects in the range of 69.5 and 67.4% on both types of phagocytes (PMNs and MNCs), respectively, at a 6.25 µg/mL concentration. The plant bark extracts showed antibacterial efficacy against Salmonella typhi	[40] [42]
Xanthium brasilicum	Moderate inhibitory activity (52.2%) was exerted by the aerial parts of Xanthium Brasilicum ethanolic extract on both types of phagocytes (PMNs and MNCs), respectively, , at a 6.25 µg/mL concentration Methanol crude extract possess highest antibacterial activity the result also showed the presence of two bioactive substances, a xanthanolide and a flavonoid.	[40] [43]
Balanites aegyptiaca	The fruits ethanolic extracts of Balanites aegyptiaca exhibited a moderate proinflammatory effect (37–40.4% increases in ROS level compared to the control) at 25–100_g/mL concentration in the case of whole blood along with PMNs phagocyte activity. The methanol extract of the fruit (edible mesocarp) of *Balanites aegyptiaca exhibited varied antibacterial and antifungal activity against all tested microorganisms, it was also showed good antioxidant properties.*	[40] [44]
Sutherlandia frutescens	The leaves Fractions from both the water extracts of 50 and 100 1C were bioactive. Fractions chosen for further studies showed that the fragment with the highest MW after the pectinase treatment had a substantially higher biological effect on complement assay than the parent molecules. Based on a comparison of the different fractions it was concluded that galactose-rich regions were important for the bioactivity, these being of the AGII and AGI type, with the latter probably being more important than the former. Fragments rich in xylose also gave higher activity than those without it. The hexane leaf extract was the most active extract against S. aureus, E. faecalis and E. coli.	[45] [46]
Hydnora abyssinica	Catechin, tyrosol and benzoic acid, 3, 4, dihydroxy-, ethyl ester compounds were isolated from Hydnora abyssinica ethanolic extract which revealed potent immunosuppressive activity against reactive oxygen species from both polymorph nuclear cells (PMNs) (45–90 % inhibition) and mononuclear cells (MNCs) (30 -65 % inhibition), T lymphocyte proliferation assay (70–93 % inhibition) as well as potent inhibitory effect against superoxide production (42–71 % inhibition) at concentrations of 6.25–100 µg/mL. Catechin was found the most potent immunosuppressive agent among all constituents examined. The root extracts (aqueous, methanol and chloroform), showed varied antibacterial and antifungal activity against 4 bacterial strains and 6 human pathogenic fungi. Aqueous extract was the most inhibitory.	[47] [48]
Astragalus membranaceus	Roots of Astragalus membranaceus (Fish.) Bge. var. mongholicus (Bge.) Hsiao (A. membranaceus) have been long used as an auxiliary reagent supporting cancer treatment. Here, we compared the chemical composition and antitumor immunomodulating activity of polysaccharides from roots of A. membranaceus (PAMs) from five major habitats in Inner Mongolia, PR China. We revealed that compositions of monosaccharides and amino acids were comparable among PAMs from different habitats. However, amounts of selenium varied widely in roots of A. membranaceus and PAMs. PAMs selenium-dependently repressed the in vivo proliferation of transplanted H22 ascitic hepatoma and S180	[49]

	sarcoma cells with low toxic impacts on tumor-bearing mice. Selenium-containing PAMs ameliorated host CD4+ T cell apoptosis and serum cytokine dysregulation induced by tumor transplantation, leading to the enhancement of cytotoxic activities of natural killer and CD8+ T cells. Moreover, PAMs also selenium-dependently improved the phagocytotic function of intra-abdominal macrophages and suppressed M2-like polarization of tumor-associated macrophages. Methanolic and Ethanolic root extracts of Astragalus membranaceus showed good inhibitory activity against diarrheal bacterial pathogens; Escherichia coli, Salmonella enteritidis, Shigella, and Campylobacter.	[50]
Menyanthes trifoliata	Polysaccharideriche fractions (PS) from Menyanthes trifoliate L. (Menyanthaceae) have been isolated. The biological tests on the immunomodulating influence with human bloodderived lymphocytes and granulocytes revealed that two fractions, B4 and B5, were strong stimulators of immune cells, whereas fractions D5 and A3 were found as potent suppressive and anti-inflammatory agents. Menyanthes trifoliata recorded antibacterial activity against Staphylococcus aureus (Mean zone of inhibition 12 ± 1.02), but non-effective as antibacterial agent against Escherichia coli and Candida albicans.	[51] [52]

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