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Review Article

# An Overview of Plant Extracts as Anti-Infectious and Anti-Complemental Tools

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## Abstract

The present work is entailed with some important aspects relating traditional plant extracts to medicinal application. In the current times so many challenges are being faced in treating some dreadful diseases especially neurodegenerative and infectious diseases. Plants are gifted by nature having potent disease fighting abilities and act as immunomodulators which is the quest of modern investigations. The scientific community is eager to link natural plant based products with antibiotic substances, immunity boosters and vaccines. From the overall survey, so many beneficial landmarks regarding the medicinal fronts have been discussed and it is to emphasize that a large section of this field is yet unexplored and should be preferentially studied to unravel their natural components as beneficiary for mankind.

**Keywords:** Anti-Complement Activity; Immunomodulation; Secondary Metabolites

## Introduction

Traditional plants are generally evaluated for their interesting biological relevance covering different studies witnessed by many recent reports [1]. Properly identified plants are separately extracted using suitable apparatus with the application of biocompatible solvents. The main objectives remain focused on to study the *in-vitro* anti-inflammatory, anti-arthritic and antimicrobial activity of target plant extracts [2]. Besides, new approaches are made to detect complement and anti-complement fascinations pertaining to this area. Depending upon the polyphosphate, synthesized by all cells, disentangling quests are practised to relate proteolytic cascade complement with the aim.

A rich source of new molecules is investigated from higher plants having pharmacological properties, which help in developing new lead compounds for novel drugs. During the last decades, the renewed interest in exploring natural products has led to the robust materials of several important drug values, viz., anticancer substances taxol, vinblastine, and vincristine or the antimalarial agent artemisinin. Success in natural products research is conditioned by careful plant selection, based on various criteria such as chemotaxonomic data, information from traditional medicine, field observation or even random collection. One of the strategies in the isolation of new lead compounds consists of bioactivity-guided isolation, in which pharmacological or biological assays are manifested to target the isolation of bioactive compounds. Hence, the tedious isolation of compounds of low interest can be avoided and a targeted isolation of new bioactive products or constituents presenting novel or unusual spectroscopic features can be undertaken. In our continuing interest towards medicinal aspects of plants [3-5], the present report has been mainly focused to review the current status of this field.

### Interdisciplinary approach: The need of hour

Metabolite profiling in crude plant extracts is not an easy measurement, since natural products display a very important structural diversity. For each compound, the orders of the atoms and stereochemical orientations have to be elucidated *de nova* in a complex manner and the compounds cannot simply be sequenced as is the case for genes or proteins. Consequently and unlike genomics and proteomics, a single analytical technique does not exist that is capable of profiling all secondary metabolites in a plant extract.

### Plant extracts as efficacious vaccines

Over the last few years, the number of emergent infectious diseases has increased at an alarming rate. In response to this increased infectious disease threat, efforts have been intensified to identify more effective, inexpensive, and more easily deliverable vaccination methods. One area of research currently under development is the genetic modification of plants for production of immunoprotective proteins [6]. Concerns and present obstacles to effective immunization [7] with plant-based vaccines for animals and humans are the active goals for meeting such demands.

Anionic antimicrobial peptides (AAMPs) have been identified in a wide variety of plant species with net charges that range between −1 and −7 and structures that include:

- Extended conformations,
- α-helical architecture
- And cysteine stabilized scaffolds [8].

These peptides commonly exist as multiple isoforms within a given plant and have a range of biological activities including the ability to kill cancer cells as well as phytopathogenic bacteria, fungi, pests, molluscs, and other predatory species. Hence, developing rapid analytical methods for bioactive components and predicting both the concentration and biological availability of nutraceutical components in foods is a topic of growing interest [9]. The outcomes of such interventions led to widespread acceptance of functional and nutraceutical foods; however, augmenting immunity is a major concern of dietary regimens [10]. Indeed, the immune system is the ultimate natural defense against undesired responses. Its proper functionality is essential to maintain the body homeostasis. Array of plants and their components hold immunomodulating properties.

### Plant-based protection against infectious diseases

Plants can serve as sources of functional antibodies used in immunotherapy [6,11]. Antibody collection is a laborious task. However, plants are engineered to produce antibodies of interesting choice to permit the isolation at high yields and at lower cost. Immunogenic peptides can be brought up in plants employing various techniques including stable transformation by bacterial pathogens (e.g., *Agrobacterium tumefaciens*), infection with engineered plant viruses, and by chemical or mechanical DNA trans-

formation methods. Among a class of strains it has been concluded that *A. nilotica, C. zeylanicum* and *S. aromaticum* can be used against multidrug resistant microbes causing nosocomial and community acquired infections [12]. Similarly the possibility of concurrent use of these antibiotics and plant extracts in treating infections caused by *E. coli* or at least the concomitant administration may not impair the antimicrobial activity of these antibiotics [13]. The increasing incidence of drug-resistant pathogens has developed interest towards compounds, obtainable from different plant oils and extracts becoming useful therapeutic tools [14].

Not only bacterial [15] and fungal infections can be treated by the application of plant extracts, infections caused by protozoan parasites, especially "Neglected Tropical Diseases" (NTDs) defined by the WHO, can be halted by plant-derived natural products as antiprotozoal leads and/or drugs in the fight against NTDs [16]. These evidences support the importance of phytochemical research based on ethnopharmacology that is considered an effective approach in the discovery of novel chemicals entities with potential as drug leads [17]. Recently such type of studies has showered plentiful knowledge to know defensive compounds understanding the functioning of plant defense systems as well [18]. Strikingly, recent experimental evidence suggests that at least some of these compounds alternatively may be involved in controlling several immune responses that are evolutionarily conserved in the plant kingdom, including callose deposition and programmed cell death [19]. Meanwhile, the solvent specification together with physio-chemical analysis has identified interesting compounds such as cyclo (D-Pro-D-Leu), cyclo(L-Pro-D-Met), cyclo (L-Pro-DPhe), cyclo (L-Pro-L-Val), 3,5-dihydroxy-4-ethyl-trans-stilbene, and 3,5-dihydroxy-4-isopropylstilbene recording good degree of antimicrobial activity [20]. In due course the antagonistic and agonistic effects may serve better tools to intensify such record.

The secondary metabolites procured from roots, leaves and flowers show effective biological activity [21]. The use of phytochemicals support practice for our immune system against infections and it is hence worthy to focus on latest developments regarding immunomodulatory activities of plants [22]. E.g. glucosinolates (GSLs) are secondary metabolites found in *Brassica* vegetables confer on them resistance against pests and diseases and the recent results in this connection indicate that GSLs and as well as extracts of different *Brassica* species, have potential to inhibit pathogen growth and offer new opportunities to study the use of *Brassica* crops in biofumigation for the control of multiple diseases [23]. In the similar fashion *Croton campestris* A., popularly known as "Velame do campo" (Euphorbiaceae), is a shrub originating from Brazil, mainly present in the Southeast and Northeast regions under the study to evaluate the antibacterial activity of the ethanol extract (EECC), hexane (HFEECC) and dichloromethane fractions (DFEECC), obtained from its leaves represent an alternative source of natural products capable of modifying and interfering with bacterial resistance to aminoglycosides [24]. Plants are accepted as rich source of secondary metabolites (SM) that exhibit a wide array of biological and pharmacological properties. Their multitarget activities may be sought agents for several clinical trials [25]. The bulk of pharmaceutically active substances viz., aldehydes, alkaloids, phenolic compounds, flavonoids, saponins, carbohydrates, proteins, lipids, glycosides, phytosterols, volatile oils, gums and mucilage and other minor phytochemicals are the inducers for obtaining good record of MIC [26,27]. Briefly, it may be stated that there is a lot yet to be done to explore anti-infectious potential of unexplored plant extracts.

## Seeking plant-based autoimmune disease vaccines

Normal individuals possess various auto-reactive T cells with the potential to escalate into autoimmune disease, peripheral T cells actively down-regulate these self-recognizing lymphocytes [28]. Environmental and/or genetic factors predispose the immune system to recognize the body's own proteins as being foreign bodies by autoimmunity [29]. An imbalance between suppressive regulation and lymphocyte activation thus shifts the outcome toward self-destruction. To overcome the autoimmune destruction, self-reactive lymphocytes are suppressed or eliminated in a process called as immunologic tolerance, including the mechanism by which a potentially injurious immune response is prevented, suppressed, or shifted to a non-injurious class of immune response" [30]. The intervened phenomena like clonal deletion, anergy (unresponsiveness), or active suppression of T cells by regulatory cytokines may be tailored by plant-based immunization.

Plant systems have been already reviewed with regard to production of vaccine sub-units [31]. The core technology of plastid transformation too, in *Chlamydomonas reinhardtii* and *Nicotiana tabacum*, on the other hand demonstrate the utility of the technology for the production of recombinant vaccine antigens [32]. In future, several other products from contained systems are expected to reach the clinical trial stage [33]. Hence, in the last few years plants have become an increasingly attractive platform for recombinant protein production [34,35]. The most relevant aspects of plant-derived vaccines that are decisive for the future development of cost effective HPV vaccines is one of the related contribution in this behalf [36]. The recent advances of plant derived vaccine antigens for the prevention of human infectious diseases have gained instant momentum [37]. E.g. Alternatives to pharmacological treatments for atherosclerosis are highly desirable in terms of cost and compliance. Identification within this approach has led to a significant trend imparting positively the field of atherosclerosis vaccination [38]. Virus-like particles (VLPs) are self-assembled derivatives from viral antigens that mimic the native architecture of viruses but lack the viral genome. Some concerns have been rationalized on the essential role of plants as a novel, speedy and economical production platform for VLP-based vaccines [39].

The history of VLP production in plants illustrates the potential of such a mode of production for human and animal medicine [40]. Ongoing efforts and challenges to producing influenza sub-unit vaccine (SUV) candidates in plants likelihood of bringing these products to the market [41] has opened worth some routes.

Recent studies have found antigen-specific proteins successfully expressed in various plant tissues and have even been tested in animals and human beings. Therefore, edible vaccines of transgenic plants have a bright future [42]. It is worthy to mention here that genetically engineered plants can be used for the biomanufacture and delivery of oral vaccines.

The relevant immunogenic properties/perspectives may be assessed under multifold examination [43,44]. In another effort to initiate the development of a plant-based vaccination model against atherosclerosis, epitopes have been found to be expressed in plants retaining immunogenicity, which opens a new path in the molecular farming field for the development of vaccines against atherosclerosis [45]. Hence, in due course use of plants to deliver vaccine candidates against viruses, bacteria, and eukaryotic parasites are focused on innovative expression strategies and the immunogenic potential of new vaccines [46-48]. In this regard, the use of plants as biofactories and delivery vehicles of TB vaccines has been researched to an elevated level [49].

Most importantly, oral vaccination using plant made antigens confers both mucosal (IgA) and systemic (IgG) immunity. In the recent past significant progress in expressing vaccine antigens in edible leaves (especially lettuce), processing leaves or seeds through lyophilization and achieving antigen stability and efficacy after prolonged storage at ambient temperatures. The oral delivery of vaccine antigens expressed in plant cells via the chloroplast or nuclear genomes and potential challenges in achieving immunity against infectious diseases using cold-chain-free vaccine delivery approaches is fascinating [50]. In some cases the generation and purification of VLPs by expressing GP5, M and N genes in *Nicotiana silvestris* plants have also been reported to justify the targeted theme [51].

In conclusion vaccines are considered as one of the greatest medical achievements in the battle against infectious diseases. However, the intractability of various diseases such as hepatitis C, HIV/AIDS, malaria, tuberculosis, and cancer poses persistent hurdles given that traditional vaccine-development methods have proven to be ineffective; as such, these challenges have driven the emergence of novel vaccine design approaches. Among the recent advances in the use of plant viruses as nanoparticle-based vaccines and adjuvants and their mechanism of action is mentionable [52]. Perspectives on how viral expression systems could allow for the development of innovative oral vaccines constituted by minimally processed plant biomass are active in this context [53]. Studies provide evidences that oral delivery of plant cells is effective in reducing antibody responses in ERT for lysosomal storage disorders facilitating further advances in clinical investigations using plant cell culture system or *in vitro* propagation [54]. Certain *in vitro* results demonstrate that the plant cells protect the recombinant protein in the gastric fluids and may enable absorption into the blood. Specifically, carrot cells containing recombinant human prGCD can be used as an oral delivery system and are a feasible alternative to intravenous administration of ERT for GD [55]. So, new technological advancements to the already existing protocols for edible vaccine development are needed [56,57].

## Complement activity

A large number of inhibitors of the complement activation had been isolated up to now from animal or plant sources [58]. The substances with the established structure can form a basis for the creation of potential medical products. However, the structures of others are still not established. The anticomplement activity of heparin for the first time has been shown in 1929 [59]. Heparin is a proteoglycan possessing anticoagulation properties. Proteoglycans belong to the largest natural molecules (å > 2 × 106 Da); including protein (5%) and carbohydrate (95%) components. The protein monomers carrying a large number of polysaccharide chains are connected with the axial molecule of hyaluronic acid. The polysaccharides found in proteoglycans usually contain acetylated aminosugars and, therefore, belong to glycosaminoglycans. Heparin is secreted to blood by mast cells of liver, lungs, and other tissues. It and the related to glycosaminoglycans [dermatan sulfate, heparin sulfate, and chondroitin sulfate] are actively investigated as complement inhibitors. Carbohydrate chains of heparin are sulfated copolymers of uronic acid and glucosamine [60]. The protein part of heparin is deleted at the preparation of glycosaminoglycan heparin. It is established that heparin blocks the interaction of C1q with complement activators, can intensify C1s inactivation under the action of C1-Inh and, in addition, inhibits the formation of C3 convertases of the alternative and classical pathways [61,62]. The ability to inhibit the formation of C3 convertase together the hemolysis inhibition completely disappears in the N- or é-desulfated heparin. It was shown that heavily sulfated low-molecular heparin derivatives prevent the rabbit myocardium damage caused by complement [63]. The devices of artificial blood circulation covered by heparin inhibit the complement activation during the surgery on heart [64].

## Synthetic low-molecular inhibitors of complement activation

At present, the application of recombinant proteins instead of traditional synthetic drugs becomes more and more attractive. The reason of this consists both in the predictability of biological properties of proteins and in the advantages of technology of the obtaining of medical products on their basis [65]. The time necessary for the design of protein preparations is less than that for the development and tests of traditional medicines. Approximately 40% of the developed protein preparations will probably become the certified medicinal preparations, whereas only 10% of new chemical substances usually become certified. One of the reasons of such a situation consists in a lower toxicity of proteins [65]. However, the problem of high cost of protein preparations becomes more and more sharp [66]. Low-molecular complement inhibitors have a number of advantages over the therapeutic pro-

tein preparations. Their cost is much lower; they better penetrate into tissues, and can be applied orally. The listed advantages become particularly important in the treatment of autoimmune disorders when a preparation should be applied for a long time. The occurrence of theoretical basics of the design of medical products as small molecules opens wide prospects in this direction [67,68].

## A danger of the treatment connected with complement inhibition

The real size of the danger arising at complement inhibition it is difficult to estimate mainly because of lack of information. It is known that the deficiency of complement is connected with an increased susceptibility to infection [69], increased sensitivity to bacterial endotoxins as a result of deterioration of their removal by the complement system [70], and autoimmune aggression, observed at system red lupus and glomerulonephritides [71]. Thus, the described effects can be assigned to potential danger of complement inhibition. As always, the question consists in a possible existence of a threshold between the extent of complement inhibition sufficient for the achievement of therapeutic effect and the inhibition resulting in complications. It was shown during the studies that 60% complement inhibition is quite enough for the achievement of success in the treatment of collagenose arthritis [71].

## Methods of substance testing for complement activity

Many natural and synthetic substances can act to some extent on the complement system at different stages of its activation cascade or directly on its components. In this connection, when developing the detection methods of the influence on complement system, it was expedient to characterize quantitatively the degree of this influence. It was important for understanding the degree of the influence and also for an estimation of working concentrations of effector, whether they are achievable in an organism and whether will exert another influence on an organism. It is well-known threshold between the medicinal and toxic action for medicinal substances. The important stages of the complement cascade are its initiation, the formation of C3 and C5 convertases, and the formation of the lytic MAC. For all these stages, except for the last (we mean the specific testing of the influence on the formation of complex and its lysis), the methods of testing are developed and described below.

## Determination of anticomplement activity

The preparations intended for intravenous administration, in particular, antibodies and other blood preparations should not possess anaphylactogenic properties. The anaphylactoid reactions arising at the intravenous introduction of preparations are as a rule caused by the activation of complement system and result in the formation of anaphylatoxins C4a, C3a, and C5a, last exhibiting the greatest activity. These anaphylatoxins cause the secretion of histamine from mast cells, which is responsible for system reaction of an organism (anaphylaxis) connected with a sharp reduction of arterial pressure, compression of bronchial tubes, etc. The anaphylactogenic properties of blood preparations can be caused by the activation of complement system due to the presence in these preparations of immune complexes and/or the aggregated immunoglobulins. This circumstance has led to development of methods of the determination of so-called anticomplement activity. The principle of these methods consists in the determination of ability of a preparation to bind the first component of complement system, and, consequently, all the methods are the modifications of the base method known under the name reaction of complement binding.

The development of ideas on the mechanisms of complement system functioning has shown that such approaches to the estimation of quality of intravenous preparations become obsolete to a certain extent. First, the binding of the first complement component itself not always leads to the system activation; on the contrary, it can inhibit such process and block the anaphylaxis development, which might be only useful. Second, the struggle with anticomplementarity of immunoglobulin preparations (e.g. by their treatment with enzymes or chemical modifiers) can lead to such their derivatives, which lose the ability to bind and activate complement system even within the immune complexes, which makes such preparations useless or even harmful (similar to blocking antibodies). Therefore, the necessity arises for a method for the quantitative determination of complement-activating activity using a comparison with easily reproduced standard [72]. For the determination of complement activating activities of preparations, a method was developed that allows the quantitative determination of the consumption of component C4 in the serum of guinea pig. The component C4 was chosen because (1) it is activated first after the binding and activation of component C1, (2) there is an amplification of the process: one activated C1 molecule can activate several C4 molecules, and (3) it is easy to follow the consumption of component C4 by a sensitive hemolytic quantitative micro method with a visual estimation without the use of photometric devices. As the standard possessing the ability to activate complement, the aggregated human immunoglobulin G was chosen; it was obtained by thermal aggregation and freed from large units by centrifugation and from monomers, by gel-filtration. The determination of activity of complement C4 component of a guinea pig is carried out with the use of the corresponding reagent R4 [72], which is a guinea pig serum free from the C4 activity, which has a high enough titer of C4 (the half lysis of sensitized sheep erythrocytes at a dilution of 1 : 2000). The difference of the method from the traditional determination of anticomplement activity consists in that determination of ability to bind and activate complement was suggested instead of the ability to bind complement only; it is more exact characteristic of properties of preparations. The determination of complement-activating abilities can be applied not only to IG preparations, but also to any substances binding complement with its subsequent activation. This method allowed the obtaining of information on the complement activation by negatively charged liposomes and the absence of appreciable activation by liposomes with a neutral charge [73]. Results agree with the data available in literature [74].

Any nucleophilic agent can be an initiator of the alternative pathway (for natural compounds, it would be a carbohydrate or a protein) possessing two important properties:

- It should be sufficiently large to bind several C3b molecules, i.e., to have some centers for creation on the surface of activator of C3 and C5 convertases

- Should not possess the negative charge necessary for binding factor H participating in the destruction of C3 convertase.

In this connection, the ability to covalently bind C3b at incubation with blood serum was considered as the criterion of the ability of the substance under study to be an activator of the alternative pathway [75].

Hence, the complement system [57] is a group of proteins that forms a central part of the innate immunity. It labels microbes and cell debris for detection and clearance by the innate and adaptive immune system and acts as an effector mechanism for the adaptive immune response.

Three distinct pathways, the classical, lectin and alternative pathway (AP), can initiate complement activation and converge at the proteolytic cleavage of complement component C3 to C3b.The complement response peaks in the formation of the membrane attack complex, a protein complex that disrupts cell membranes, thus lysing the targeted cell. While the classical and lectin pathway recognize antibody deposits and bacterial carbohydrates, respectively, the AP is activated by spontaneous hydrolysis and covalent attachment of C3b to adjacent cell surfaces [76,77]. Unlike most pathogens, host cells express membrane-bound complement inhibitors to prevent their destruction by the complement system [78]. The most important plasma inhibitor of the complement system is factor H (FH), which both regulates complement activation in solution and specifically binds to and protects host cells [79]. It is a linear, ~155 kDa glycoprotein and consists of twenty globular domains called complement control protein (CCP) or short consensus repeat (SCR; alternatively, short complement regulator) domains [80]. FH inhibits the complement cascade by blocking activating binding sites in C3b and acting as cofactor for factor I, a serum protease that cleaves and inactivatesC3b [81,82]. The N-terminal domains of FH, CCP1-4, bind to C3b and contain the primary complement-regulating activity, while a second major binding site for C3b has been mapped to CCP19-20 [83]. Flexible peptide linkers between the CCPs allow the protein chain to fold back on itself. This enables FH to bind a single C3bmolecule with both the N- and C-terminus, thereby increasing the avidity of the interaction [84]. Furthermore, FH contains two heparan sulfate (HS)-binding sites, one localized to CCP7 and another to CCP19-20 [83]. HS are linear, sulfated polysaccharides of the glycosaminoglycan (GAG) family that are present on host cell surfaces and in basement membranes, but absent on microbes [85]. Their recognition by FH is assumed to be the principal mechanism for host-pathogen differentiation [79]. Interactions with HS in base membranes, such as the glomerular basement membrane in the kidney or Bruch's membrane in the eye, are particularly important for complement control due to the absence of membrane-bound complement inhibitors. Aside from C3b and HS, interactions of FH with various other ligands have been described and recently reviewed in great detail [86], including self-association of two or more FH molecules. In humans, complement regulation by FH is further influenced by the presence of the structurally similar FH-like protein 1 and FH-related proteins 1–5. FH-like protein 1is generated through alternative splicing and includes the seven N-terminal domains of FH, thus containing both the CCPs with regulatory activity and the ligand binding sites in CCP7 [87]. FH-related proteins resulted from gene duplication events and consist of four to nine CCPs with high homology toCCP6-9 and CCP19-20 of FH. Except for FH-related protein 5, they lack a direct regulatory function [88]. However, FH-related proteins 3 and 4 have been found to enhance the cofactor activity of FH, whereas FH-related protein 1 is believed to compete with FH for cell surface ligands [89]. Detailed description of these proteins is beyond the scope of this review and has been done previously [90].

## Future Strategy

New compounds with high levels of pharmacological activity are urgently required for a wide range of human disorders and diseases. A number of scientific publications showed that plants contain several nutritional and functional compounds, but the current state of knowledge is still far from satisfactory. However, their activity as chemo-preventive and anti-inflammatory, antidiabetic, anticancer, needs further investigation. Eventually my personal suggestion to those companies which are involved in production and merchandise of medicinal plants should provide relevant information regarding bioactive components present in plants.

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## Bibliography

1. Kumar D., *et al*. "Evaluation of antioxidant activity of selected Indian medicinal plants". *Journal of Fundamental and Applied Sciences* 2 (2014): 1-10.

2. Rahman H., *et al*. "*In-vitro* Anti-inflammatory and Anti-arthritic Activity of Oryza sativa Var. Joha Rice (An Aromatic Indigenous Rice of Assam). American-Eurasian". *Journal of Agriculture and Environmental Sciences* 15 (2015): 115-121.

3. Iqbal J., *et al*. "Antidermatophytic Activity of Angiospermic Plants: A Review". *Asian Journal of Pharmaceutical and Clinical Research* 8 (2015): 75-80.

4. Mishra R P., *et al.* "Isolation and Purification of a Galactose Specific Lectin from Seeds of Bauhinia variegata and Evaluation of its Antimicrobial Potential". *IJPSR* 7.2 (2016): 804-809.

5. Mishra R P., *et al*. "Biological Evidential Panorama of Lectins: Their Isolation, Purification and Applications". *World Journal of Pharmaceutical Research* 5 (2016b): 1661-1689.

6. James E C III and William HRL. "Plant-Based Vaccines for Protection Against Infectious and Autoimmune Diseases". *Critical Reviews in Plant Sciences.* 21.2 (2002): 93-109.

7. Wasserman RL. "A new intravenous immunoglobulin (BIVIGAM) for primary humoral immunodeficiency: Expert Rev". *Journal of Clinical Immunology* 10 (2014): 325-337.

8. Prabhu S., *et al.* "Anionic Antimicrobial and Anticancer Peptides from Plants". *Critical Reviews in Plant Sciences* 32 (2013): 303-320.

9. Xiaonan LU and Barbara A Rasco. "Determination of Antioxidant Content and Antioxidant Activity in Foods using Infrared Spectroscopy and Chemometrics: A Review". *Critical Reviews in Food Science and Nutrition* 52.10 (2012): 853-875

10. Joseph SV., *et al*. "Fruit polyphenols: a review of anti-inflammatory effects in humans". *Critical Reviews in Food Science and Nutrition* 56.3 (2016): 419-444.

11. Hiatt A., *et al*. "Production of antibodies in transgenic plants". *Nature* 342 (1989): 76-78.

12. Rosina K., *et al*. "Antimicrobial Activity of Five Herbal Extracts Against Multi Drug Resistant (MDR) Strains of Bacteria and Fungus of Clinical Origin". *Molecules* 14 (2009): 586-597.

13. Rula M Darwish and Talal A Aburjai. "Effect of ethnomedicinal plants used in folklore medicine in Jordan as antibiotic resistant inhibitors on Escherichia coil". *BMC Complementary and Alternative Medicine* 10 (2010): 10-19.

14. Dianella Savoia. "Plant-derived antimicrobial compounds: alternatives to antibiotics". *Future Microbiology* 7.8 (2012): 979-990.

15. Vishvanath T., *et al.* "Antimicrobial active herbal compounds against Acinetobacter baumannii and other pathogens". *Frontiers in Microbiology* 6 (2015): 618.

16. Schmidt T J Khalid., *et al*. "The potential of secondary metabolites from plants as drugs or leads against protozoan neglected diseases- Part I". *Current Medicinal Chemistry* 19.4 (2012): 2128-2175.

17. Brusotti G., *et al.* "The role of analysis in the ethnopharmacological approach". *Journal of Pharmaceutical and Biomedical Analysis* 87 (2014): 218-228.

18. Geedhu Daniel and Krishna Kumari S. "Quantitative Analysis of Primary and Secondary Metabolites in aqueous hot extract of Eugenia uniflora (L.) Leaves". *Asian Journal of Pharmaceutical and Clinical Research* 8.10 (2015): 334-338.

19. Anna Piasecka., *et al.* "Secondary metabolites in plant innate immunity: conserved function of divergent chemicals". *New Phytologist* 206 (2015): 948-964.

20. Tania E Sorto-Gomez., *et al.* "Effect of fish oil on glutathione redox system in multiple sclerosis". *American Journal of Neurodegenerative Disease* 5.2 (2016): 145-151.

21. Meret H., *et al.* "Identification, quantification, spatiotemporal distribution and genetic variation of major latex secondary metabolites in the common dandelion (Taraxacum officinale agg.)". *Phytochemistry* 115 (2015): 89-98.

22. Hina Y., *et al.* "Immunomodulators from Plant Source: A Review". *World Journal of Pharmacy and Pharmaceutical Sciences* 4.8 (2015): 21-36.

23. Sotelo T., *et al*. "*In Vitro* Activity of Glucosinolates and Their Degradation Products against Brassica-Pathogenic Bacteria and Fungi". *Applied and Environmental Microbiology* 8.1 (2015): 432-440.

24. Henrique DMC., *et al.* "In vitro Potentiation of the Aminoglycoside Antibiotic Activity by Croton campestris A. Against Multiresistant Bacteria". *TBAP* 5.5 (2015): 322-330.

25. Michael W. "Modes of Action of Herbal Medicines and Plant Secondary Metabolites". *Medicines* 2.3 (2015): 251-286.

26. Umer Q., *et al.* "Preliminary phytochemical screening and *in vitro* antibacterial activity of Anamirta cocculus (Linn.) seeds". *Journal of King Saud University - Science* 27.2 (2015): 97-104.

27. An-Ran W., *et al.* "Secondary Metabolites of Plants from the Genus Chloranthus: Chemistry and Biological Activities". *Chemistry and Biodiversity* 12.4 (2015): 451-473.

28. Jean-Francois B and Lucienne C. "Tolerance to islet autoantigens in type 1 diabetes". *Annual Review of Immunology* 19 (2001): 131-161.

29. Luppi P., *et al*. "Genetic background and environment contribute synergistically to the onset of autoimmune diseases". *Journal of Molecular Medicine* 73.8 (1995): 381-393.

30. Weiner HL. "Oral tolerance, an active immunologic process mediated by multiple mechanisms". *Journal of Clinical Investigation* 106.8 (2000): 935-937.

31. Stephen JS and John AH. "Plant-based vaccines". *International Journal for Parasitology* 33.5 (2003): 479-493.

32. Teodoro C., *et al*. "Chloroplasts as expression platforms for plant-produced vaccines". *Expert Review of Vaccines* 9.8 (2010): 893-911.

33. Rosella F., *et al*. "Plant-derived vaccines and other therapeutics produced in contained systems". *Expert Review of Vaccines* 9.8 (2010): 877-892.

34. Vidadi Y., *et al.* "Clinical development of plant-produced recombinant pharmaceuticals Vaccines, antibodies and beyond". *Human Vaccines* 7.3 (2011): 313-321.

35. Maziar HP and Saeid Z. "Plant-based recombinant vaccines". *International Journal of Agriculture and Crop Sciences* 6.1 (2013): 27-30.

36. Mohammad TW., *et al.* "Plant-derived vaccines An approach for affordable vaccines against cervical cancer". *Human Vaccines and Immunotherapeutics* 8 (2012): 1-4.

37. Ravindra BM., *et al*. "Recent advances in plant derived vaccine antigens against human infectious diseases". *Research in Pharmacy* 2.2 (2012): 08-19.

38. Jorge A., *et al*. "A perspective for atherosclerosis vaccination: Is there a place for plant-based vaccines". *Vaccine*. 31.10 (2013): 1364- 1369.

39. Qiang C and Huafang L. "Plant-derived virus-like particles as vaccines". *Human Vaccines and Immunotherapeutics* 9.1 (2013): 26-49.

40. Nunzia S and Edward PR. "Virus-like particles produced in plants as potential vaccines". *Expert Review of Vaccines* 12.2 (2013): 211-224.

41. Vidadi Y., *et al.* "Advances and challenges in the development and production of effective plant based influenza vaccines". *Expert Review of Vaccines* 14.4 (2014): 519-535.

42. Zheng-jun G., *et al.* "Recent advances and safety issues of transgenic plant-derived vaccines". *Applied Microbiology and Biotechnology* 97.7 (2013): 2817-2840.

43. Sergio Rosales-Mendoza and Jorge A Salazar-Gonza´lez. "Immunological aspects of using plant cells as delivery vehicles for oral vaccines". *Expert Review of Vaccines* 13.6 (2014): 737-749.

44. Tatsuhiko A., *et al.* "Novel Transgenic Rice-Based Vaccines". *Archivum Immunologiae et Therapiae Experimentalis* 63.2 (2015): 87-99.

45. Jorge A Salazar-Gonzalez., *et al*. "Production of a Plant-Derived Immunogenic Protein Targeting ApoB100 and CETP: Toward a Plant-Based Atherosclerosis Vaccine". *Molecular Biotechnology* 56.12 (2014): 1133-1142.

46. Marisela H., *et al.* "Transgenic plants: a 5-year update on oral antipathogen vaccine development". *Expert Review of Vaccines* 13.12 (2014): 1523-1536.

47. Jacqueline M., *et al*. "Bringing plant-based veterinary vaccines to market: Managing regulatory and commercial hurdles". *Biotechnology Advances* 33.8 (2015): 1572-1581.

48. Pit SL and Mohd Hair-Bejo. "Farming of Plant-Based Veterinary Vaccines and Their Applications for Disease Prevention in Animals". *Advances in Virology* (2015): 1-12.

49. Sergio Rosales-Mendoza., *et al*. "An overview of tuberculosis plant-derived vaccines". *Expert Review of Vaccines* 14.6 (2015) 877-889.

50. Hui-Ting C and Henry D. "Plant-made oral vaccines against human infectious diseases-Are we there yet". *Plant Biotechnology Journal* 13.8 (2015): 1056-1070.

51. Laura Uribe-Campero., *et al*. "Plant-based porcine reproductive and respiratory syndrome virus VLPs induce an immune response in mice". *Research in Veterinary Science* 102 (2015): 59-66.

52. Marie-Ève L., *et al.* "Plant Viruses as Nanoparticle-Based Vaccines and Adjuvants". *Vaccines* 3 (2015): 620-637.

53. Jorge A., *et al.* "Current status of viral expression systems in plants and perspectives for oral vaccines development". *Plant Molecular Biology* 87.3 (2015): 203-217.

54. Jin S., *et al*. "Oral delivery of Acid Alpha Glucosidase epitopes expressed in plant chloroplasts suppresses antibody formation in treatment of Pompe mice". *Plant Biotechnology Journal* 13.8 (2015): 1023-1032.

55. Yoseph S., *et al*. "Plant-based oral delivery of b-glucocerebrosidase as an enzyme replacement therapy for Gaucher's disease". *Plant Biotechnology Journal* 13.8 (2015): 1033-1040.

56. Anjali A., *et al*. "New Strategies Toward Edible Vaccines. An Overview". *Journal of Dietary Supplements* 11 (2016): 1-16.

57. Loevena MA., *et al.* "The role of heparan sulfate as determining pathogenic factor in complement factor H-associated diseases". *Molecular Immunology* 63.2 (2015): 203-208.

58. Kozlov LV., *et al.* "Artificial Inhibition of the Complement System". *Bioorganicheskaia Khimiia* 33.5 (2007): 485-510.

59. Ecker EE and Gross P. "Anticomplementary power of heparin" *Journal of Infectious Diseases* 44.3 (1929): 250-253.

60. Jaques LB. "Heparins--anionic polyelectrolyte drugs". *Pharmacological Reviews* 31 (1979): 99-166.

61. Wuillemin WA., *et al*. "Potentiation of C1 inhibitor by glycosaminoglycans: dextran sulfate species are effective inhibitors of *in vitro* complement activation in plasma". *Journal of Immunology* 159.4 (1997): 1953-1960.

62. Kirschfink M., *et al.* "Secreted chondroitin sulfate proteoglycan of human B cell lines binds to the complement protein C1q and inhibits complex formation of C1". *Journal of Immunology* 158.3 (1997): 1324-1331.

63. Gralinski MR., *et al.* "LU 51198, a Highly Sulfated, Low-Molecular-Weight Heparin Derivative, Prevents Complement-Mediated Myocardial Injury in the Perfused Rabbit Heart" *Journal of Pharmacology and Experimental Therapeutics* 282 (1997): 554-560.

64. Velthuis H., *et al.* "Specific complement inhibition with heparin-coated extracorporeal circuits". *Annals of Thoracic Surgery* 61.4 (1996): 1153-1157.

65. Buckel P. "Recombinant proteins for therapy". *Trends in Pharmacological Sciences* 17.12 (1996): 450-456.

66. Grindley J N and Ogden J E. "Forecasting the future for protein drugs". *Script Magazine* 11 (1995): 53-56.

67. Verlinde CLM and Hol WGJ. "Structure-based drug design: progress, results and challenges". *Structure* 2.7 (1994): 577-587.

68. Hruby VJ. "Prospects for peptidomimetic drug design". *Drug Discovery Today* 2.5 (1997): 165-167.

69. Wetsel RA and Colten HR. "The molecular biology of complement deficiency syndromes". In Kluwer Academic, Norwell (1990): 401-429.

70. Fischer MB., *et al.* "Increased susceptibility to endotoxin shock in complement C3- and C4-deficient mice is corrected by C1 inhibitor replacement". *Journal of Immunology* 159.2 (1997): 976-982.

71. Wang Y., *et al.* "Anti-C5 monoclonal antibody therapy prevents collagen-induced arthritis and ameliorates established disease". *Proceedings of the National Academy of Sciences of the United States of America* 92.19 (1995): 8955-8959.

72. Kozlov LV and Guzova VA. "Opredelenie komplementaktiviruyushchei aktivnosti preparatov dlya vnutrivennogo vvedeniya. Metodicheskie rekomendatsii no. 98/87 (Determination of Complement-activating Activity of Preparations for Intravenous Administration: Methodological Advices no. 98/87), Moscow: Minzdrav RF (1998).

73. Kozlov LV., *et al.* "Action of nonviral gene delivery vectors on human complement system: low anticomplementary activity of lipoplexes based on lacZ plasmid and phospholipid/oligocation liposomes". *Cytobios* 106 (2001): 67-74.

74. Chonn A., *et al.* "The role of surface charge in the activation of the classical and alternative pathways of complement by liposomes". *Journal of Immunology* 146.12 (1991): 4234-4241.

75. Kozlov LV., *et al.* "RF Patent 2195664". Byull Izobret (2002) 36.

76. Law SK and Levine RP. "Interaction between the third complement protein and cell surface macromolecules". *Proceedings of the National Academy of Sciences of the United States of America* 74.7 (1977): 2701-2705.

77. Pangburn MK., *et al*. "Formation of the initial C3 convertase of the alternative complement pathway. Acquisition of C3 b-like activities by spontaneous hydrolysis of the putative thioester in native C3". *Journal of Experimental Medicine* 154.3 (1981): 856-867.

78. Zipfel PF and Skerka C. "Complement regulators and inhibitory proteins". *Nature Reviews Immunology* 9 (2009): 729-740.

79. Pangburn MK. "Host recognition and target differentiation by factor H, a regulator of the alternative pathway of complement". *Immunopharmacology* 49.1 (2000): 149-157.

80. Schmidt CQ., *et al.* "Translational mini-review series on complement factor H: structural and functional correlations for factor H". *Clinical and Experimental Immunology* 151.1 (2008a): 14-24.

81. Harrison RA and Lachmann PJ. "The physiological breakdown of the third com-ponent of human complement". *Molecular Immunology* 17.1 (1980): 9-20.

82. Weiler JM., *et al.* "Control of the amplification convertase of complement by the plasma protein beta1H". *Proceedings of the National Academy of Sciences of the United States of America* 73 (1976): 3268-3272.

83. Schmidt CQ., *et al.* "A new map of glycosaminoglycan and C3bbinding sites on factor H". *Journal of Immunology* 181.4 (2008): 2610-2619.

84. Morgan HP., *et al.* "Structural basis for engagement by complement factor H of C3b on a self-surface". *Nature Structural and Molecular Biology* 18.4 (2011): 463-470.

85. Sarrazin S., *et al.* "Heparan sulfate proteoglycans". *Cold Spring Harbor Perspectives in Biology* 3.7 (2011).

86. Perkins SJ., *et al.* "Complement fac-tor H-ligand interactions: self-association, multivalency and dissociation constants". *Immunobiology* 217.2 (2012): 281-297.

87. Zipfel PF and Skerka C. "FHL-1/reconectin: a human complement and immuneregulator with cell-adhesive function". *Immunology Today* 20.3 (1999): 135-140.

88. McRae JL., *et al.* "Human factor H-related protein 5 has cofactor activity, inhibits C3 convertase activity, binds heparin and C-reactive protein, and associates with lipoprotein". *Journal of Immunology* 174.10 (2005): 6250-6256.

89. Hellwage J., *et al.* "Functional properties of complement factor H-related proteins FHR-3 and FHR-4: binding to the C3d region of C3b and differential regulation by heparin". *FEBS Letters* 462.3 (1999): 345-352.

90. Jozsi M and Zipfel PF. "Factor H family proteins and human diseases". *Trends in Immunology* 29.8 (2008): 380-387.

**Volume 2 Issue 2 February 2018**