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THE ERA OF PLANT BASED MEDICINE- AN OVERVIEW

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ABSTRACT
The present work is an overview of the important aspects relevant to the traditional plant extracts of biomedical application. The present era is facing so many challenging scenario in treating many dreadful diseases especially neurodegenerative and infectious diseases. Besides their disease fighting abilities, their use as immunomodulators is the quest of current times. From the overall studies so many beneficial landmarks regarding the medicinal relevant plant extracts is made and it is to emphasize that the more and more investigations should be opened to unravel their natural components to be beneficiary for mankind.

1. INTRODUCTION

Traditional plants are generally evaluated for their ineresting biological relevance covering different studies witnessed by many recent reports.[1] Properly identified plants are separately extracted using suitable apparatus with the application of reliable 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 anticomplement 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. Many findings have been reported to establish the complex relationship between coagulation and innate immunity.[3] In some cases, evaluations are made to quantitatively assess primary metabolites and secondary metabolites in aqueous hot shoot/root extracts. The main aim lies in finding plant associated extracts that could be a potential source of natural antioxidant to stem their essence as therapeutic agents in preventing various diseases.[4] Anti-diabetic and anti-helmintics are also correlated to evaluate various fruit extracts. The anti-diabetic activity is determined by inhibition of haemoglobin glycation method. Phytochemical constituent like ascorbic acid, β-carotene and lycopene are also determined to reveal that certain fruit extracts have the ability to inhibit the glycation of haemoglobin. In another recent report ethanolic extract of the whole plant of *A. indicum* Linn has been found to pursue significant anti-inflammatory activity in a dose dependent manner comparable to the reference standard ibuprofen.[5] The anti-inflammatory activity and the mechanism of action of certain plant extracts is still a case of garbing considerable attraction.[6-8] One of the interesting assets dealing with the same area of research is to find the effect of age, season and growth conditions on anti-inflammatory activity in some plant extracts.[9] From the series of experiments conducted, it has been shown that growing the plants under conditions of stress (high temperature, high light intensity), or with addition of fertilizer, results in reduced amounts of anti-inflammatory compounds being accumulated.

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. One major drawback of this strategy is the frequent isolation of known metabolites. Therefore, metabolite profiling using hyphenated techniques such as LC/UV, LC/MS and more recently LC/NMR rapidly provides plenty of structural information, leading to a partial or a complete online *de nova* structure determination of the natural products of interest. On the other hand bioassays performed after LC/micro fractionation of the extracts allow an efficient localization of the bioactive LC-peaks in the chromatograms. 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.

2. Interdisciplinary Approach: The Need of Hour

In order to discover new bioactive compounds from plant source that could become new leads or new drugs, extracts should be submitted at the same time to a chemical screening and to various biological or pharmacological targets. The chemical screening or metabolite profiling is aimed at distinguishing between already known compounds (dereplication) and new molecules directly in crude plant extracts. Thus, the tedious isolation of known compounds can be avoided and a targeted isolation of constituents presenting novel or unusal spectroscopic features can be undertaken. It has to be noted that metabolite profiling clearly refers here to the detection and identification of plant metabolites and is different from the metabolic profiling process associated with detection of metabolites issued from a given new lead compound. Considering the achievements that have been put forth by the related study as discussed above "Isolation and Identification of Secondary Metabolites from Selected Medicinal Plants. And Assessment of their Anti-complement and Antioxidant Properties", has been aimed.

Metabolite profiling in crude plant exracts is not an easy 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. Consrequently and unlike genomics and proteomics, a single analytical technique does not exist that is capable of profiling all secondary metabolites in a plant extract. In order to develop innovative strategies for the metabolite profiling of crude plant extracts, advantage has been taken of the extraordinary development of hyphenated techniques (and paricularly LC/MR and LC/NMR) over the last decade for studing their possible application in literature have been dedicated to these powerful methodologies. Emphasis will be put on the strategy developed for efficient dereplication of natural products and for the on-line identification of bioactive constituents based on the combination of LC/UV-DAD, LC/MS, LC/MS/MS and LC/NMR applied to crude plant extract screening. The role of these techniques in the structural investigation of unstable products, or compounds that are diffcult to isolate at the preparative level to be highlighted by different examples of application is thus the need of the current times.

3. Plant Extracts the Efficaceous 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.[10] Concerns and present obstacles to effective immunization[11] 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.[12] 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.[13] The outcomes of such interventions led to widespread acceptance of functional and nutraceutical foods; however, augmenting immunity is a major concern of dietary regimens.[14,15] 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.

3.1. Plant-Based Protection Against Infectious Diseases

Plants can serve as sources of functional antibodies used in immunotherapy.[29,10] Antibody collection is a laboursome 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 transformation methods.

3.2. Seeking Plant-Based Autoimmune Disease vaccines

Normal individuals possess various autoreactive T cells with the potential to escalate into autoimmune disease, peripheral T cells actively down-regulate these self-recognizing lymphocytes.[30] Environmental and/or genetic factors predispose the immune system to recognize the body's own proteins as being foreign bodies by autoimmunity.[31] 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 noninjurious class of immune response".[32] The intervened phenomena like clonal deletion, anergy (unresponsiveness), or active suppression of T cells by regulatory cytokines may be tailored by plant-based immunization.

3.3. Intravenous Immunoglobulin

It has been reported that decrease in hemolytic complement activity is observed in all patients who experience adverse reactions. The decrease may be attributed to binding and activating complement (anticomplement activity) by IgG aggregates. The anticomplement activity could be eliminated by reduction, ultracentrifugation and alkylation, digestion with proteolytic enzymes or incubation at pH 4.[43] The aim to reduce anticomplement activity and to preserve intact IgG, led some manufacturers to treat with less pepsin for shorter periods[33], to use the more specific enzyme plasmin[34] and to treat with chemical reagents. Today, most commercial IVIGs are produced from large plasma pools (1000 or more donors) by first using cold ethanol fractionation to collect the IgG fraction.

Considering above aspects the current times demand to explore the immunomodulation actions of traditional plants to achieve the laboursome task at low cost and less time. For instance, *Purple Coneflower (Echinacea)* is one of the most important plants having various herbal preparations that purport to improve immune functioning (35). Alkyl amides present in *Echinacea* sp. have reported to possess immunomodulatory actions as they suppress the ability of activated Jurkat T cells (key mediators of antiviral immunity) to produce IL-2 independently (36; 37). Arabinogalactan-protein and various other bioactive constituents of this plant have been clearly identified as stimulators of both the classical and alternative pathway of complement activation and modulation involving inhibition or stimulation of immunity.

4. Complement and Anticomplement Studies Using Plant Extracts: A Novel Strategy

Complement is a potent innate immune defense against microbes.[16] Neurodegenerative diseases have provoked so many groups to link the present area of study to gain momentum in treating disorders of such class. Autism spectrum disorders (ASDs) represents a heterogeneous group of neurodevelopmental disorders. As a critical component of the innate immune response, the complement system comprises both directly acting factors and factors that augment other components of the immune system.[17] Recent studies suggest involvement of complement component C1q in fundamental neurodevelopmental pathways and in maintenance and elimination of dendrites and synapses.[17] Such type of studies is also contributory in tracking anti-cancer elements.[18] The immune enhancing effect of certain plants has also attained considerable attention to develop formulations for a strong complement system.[19-21] In some cases folk medicine has been reported to be used for treatment of excessive complement activation.[22] for instance, *Cinnamon*- as a folk medicine, has been traditionally applied for the treatment of inflammatory disorders and gastric diseases. After molecular analysis of the plant its components have found efficient biological activities including antimicrobial, antiviral, antioxidant, antitumor, antihypertension, antilipemic, antidiabetes, gastroprotective and immunomodulatory as has been reported by many workers.[23] All it is because of the fact that great number of natural substances affect the complement system in addition to its natural regulators.[24-26] To explore the biomedical applications of target plants to detect their immunoefficient effect is thus attaining higher order of research interst.[27,28]

4.1. Complement Activity

A large number of inhibitors of the complement activation had been isolated up to now from animal or plant sources.[24] 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.[56] Heparin is a proteuglycan 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 it glucosaminoglycans [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.[57] The protein part of heparin is deleted at the preparation of glucosaminoglycan 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.[58,59] 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.[60] The devices of artificial blood circulation covered by heparin inhibit the complement activation during the surgery on heart.[61]

4.2. 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.[62] 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.[62] However, the problem of high cost of protein preparations becomes more and more sharp.[63] Low-molecular complement inhibitors have a number of advantages over the therapeutic protein 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.[64,65]

4.3. 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[66], increased sensitivity to bacterial endotoxins as a result of deterioration of their removal by the complement system [67], and autoimmune aggression, observed at system red lupus and glomerulonephritides.[66] Thus, the described effects can be assiggned 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 arthritises.[68]

4.4. Prospects of Anticomplement Medicinal Preparations

The study of complement inhibitors, in particular, sCR1 and anti-C5 MAbs (nos. 1 and 12 in Table 1) gives a convincing proof of that the complement inhibition can not only prevent the development of diseases, but also ease the course of some of them. The preparations sCR1 (no. 1 in Table 1) and anti-C5 MAb (5G1.1 and 5G1.1-scFv, nos. 12 and 14 in Table 1) are now under clinical trials and show encouraging results at the treatment of various diseases and disturbances. Undoubtedly, their application as antcomplement preparations can reduce clinical heaviness of some diseases. However, as already mentioned, the preparations on the basis of recombinant proteins (the most part of preparations in Table 1) can appear economically unprofitable[63], and, in long-term prospects, the cheaper complement inhibitors for oral application will be developed. Now several laboratories of the world are occupied with the development of low-molecular complement inhibitors with desirable pharmacological properties, and one should not doubt that these works will lead to a creation of so necessary preparations.

4.5. 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.

5. Plant based Supplemental and Medicinal Aspects

The main asset to chronic disease development in modern lifestyle is inflammation.[15] Inflammation involves age-related degenerative diseases of nearly every organ system peripherally and centrally, including the most well-known and globally pervasive: cardiovascular diseases (CVD), cancer, and Alzheimer's disease.[38,39] Such dreadful diseases need to be treated using plant based medicinal plans. In addition, plant-derived foods or beverages, such as red wine, cocoa and tea have limited or no fiber or essential nutrients yet impart beneficial biological effects when consumed.[40, 41] Plant components thus represent health benefits; many of which have been chemically characterized and fall into the large family of compounds known as polyphenols.

5.1. Anti-Inflammatory Effects

Effects of fruits on meal-induced inflammation (42-48) have been thouroughly updated. The number of studies investigating the anti-inflammatory effects of long-term consumption of polyphenol-rich fruits in humans is relatively limited compared to the vast amounts of evidence from *in vitro* and *in vivo* animal studies. Many of them have entered into relative clinical trials.[43,51] It has been found that daily intake of strawberries would improve fasting indices of inflammation.[50] Chronic human studies on blueberries and inflammation have been reported in 4 recent publications.[52-54] A considerable amount of animal and *in vitro* data indicates that blueberries consumption may have a beneficial impact on various CVD risk factors, including inflammatory status.[49] conducted a single blinded, parallel arm study in which 48 men and women with MetS consumed 50 g of freeze dried blueberry powder (equivalent to 350 g of the fresh fruit) in the form of a water-based beverage.

5.2. Antidiabetic Activity by Phytochemicals

Plant based extracts are possessing well pronounced antidiabetic activity as a result of the presence of certain very important active principles and minerals in these plants that include terpenoids, alkaloids, phenolics, flavonoids, saponins, carbohydrates, cardiac glycosides, copper, zinc and manganese (88; 90-96). Various mechanism of action through which their effects are exhibited include promoting regeneration of cells of islets of Langerhans in the pancreas as exhibited by *Pterocarpus marsupium*. Enhancement of insulin release and activity on the cells as exhibited by *O. europea* L. olive leaf. Decrease in peripheral glucose uptake at the duodenal cellular level and other aspects of small intestine exhibited by *M. indica* and *O. europea* L. olive leaf extracts. Restricting the rise of blood glucose levels caused by pituitary hormones have been shown to be responsible for inhibiting peripheral utilization of glucose as well as glycogenolysis exhibited by *Gymnema sylvestre*, and the presence of high level of fiber in plants which interferes with carbohydrate absorption.[97-100]

5.3. Plant Based Analgesic Activity

In some cases plant extracts have been found more efficacious analgesic agents than morphine[19], yet non-addictive and also proved to be non-toxic.[101] Similar findings were also reported[102] in the alcoholic extract of some fruits. The analgesic activity of noni fruit puree on mice has been found more pronounced than tramadol. The findings suggest that the preparations of noni fruits are effective in decreasing pain and joint destruction caused by arthritis.[529]

5.4. Anxiolytic activity by Plant Extracts

Anxiety disorders have been the challenge to the modern era. Recent research has demonstrated the effects of fruit on preventing anxiety disorders, affecting an estimated 25% of the adult population at some point during their lifetime.[103] Methanol crude extract of fruit showed significant affinity to the gamma-amino butyric acid A (GABAa), the commonest inhibitory neurotransmitter in the central nervous system and displayed 75% binding inhibition as an agonist and thus induce its anxiolytic and sedative effects.

5.5. Estrogenic and anti-estrogenic activity

It has been reported that *M. citrifolia* have very weak *in vivo* estrogenic activity. According to[105], the relative estrogenic potency of alcohol and water extracts of *M. citrifolia* was 1:1,000 and 1:10,000 respectively, indicating that the estrogenic activity is only seen at low doses, and even then it has very low potency in comparison to estradiol, suggesting that the beneficial effects of noni are not closely linked to estrogen mediated action. On the other hand anti-estrogenic effect of methanolic extracts of *Abutilon indicum* on uterotropic and uterine peroxidase activities in ovariectomized rats has been studied.[55] The extract has been found to cause significant suppression of enzyme activity as well as uterotropic response induced by estradiol.

5.6. Wound and Cardiovescular

The ethanolic extract of *Abutilon indicum* has been studied for wound healing activity-using incision, excision and dead space wound models in albino rats.[55] The extract at a dose of 400-mg/kg showed significant increase in wound contraction rate, skin breaking strength, granuloma strength and dry granuloma weight. Moreover, the decrease in epithelisation period was observed as compared to control and standard. This pro-healing was dedicated to increase in collagenation deposition as well better alignment and maturation.[106]

5.7. Other Effects

Recently, it has been reported that noni juice contains angiotensin-I-converting enzyme (ACE).[107] Since ACE is commonly prescribed to treat high blood pressure, therefore this can be recognized as a therapeutical intervention for lowering blood pressure. Recent research has demonstrated the effects of noni fruit on preventing arteriosclerosis, a disease related to the oxidation of low density lipoproteins (LDL). Methanol and ethyl acetate extracts showed with the thiobarbituric acid reactive substance method 88 and 96% inhibition, respectively, of copper-induced LDL oxidation. This beneficial effect could be due to the presence of lignans, phenylpropanoid dimers.[108] 5-lipoxygenase and 15-lipooxygenase are responsible for production of leukotrienes that instigate asthmatic and allergic reactions and act to sustain inflammatory reactions.[19] Recent research has showed the role of 5- lipoxygenase in cardiovascular and neuropsychiatric illnesses.[129] Oxidation of LDL has been recognized as playing an important role in the initiation and progression of atherosclerosis. Methanol and ethyl extract of fruit showed 88 and 96% inhibition, respectively of copper-induced oxidation of low density lipoprotein particles *in vitro*. Six lignans were isolated from ethyl extract of the fruit and has been showed to have inhibiting effect of copperinduced LDL oxidation in a dose-dependent manner.[108, 104] isolated two new lignans, (+)- 3,4,3',4'-tetrahydroxy-9,7'alpha-epoxylignano-7 alpha,9'- lactone and (+)-3,3'-bisdemethyltanegool as well as seven known compounds from the fruits which are responsible for inhibition of 5- or 15-lipoxygenase.[109] Two new anthraquinones,1,6-dihydroxy-5-methoxy-2methoxy methyl anthrax quinone (1) and 1,5,7-trihydroxy-6- methoxy-2-methoxy methyl anthrax quinone (2), and one new lignan isoamericanoic acid A (3) were isolated from the fruits of *M. citrifolia* along with 11 known compounds[110] Recently, it has been reported that antispasmodic and vasodilatory activities of *M. citrifolia* root extract are mediated through blockade of voltage-dependent calcium channels and it showed antidyslipidemic effects and it can be used as a potential medicine for cardiovascular diseases. However, further studies are required to prove the safety and efficacy of *M. citrifolia* and its constituents in actual clinical settings.[111]

6. 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 chemopreventive and anti-inflammatroy, antidibetic, anticancer, needs further investigation. A drug development programme should be undertaken to develop modern drugs with the compounds isolated from these plants, but before that, a comprehensive phytochemical profiling, extensive investigation of their bioactivity, mechanism of action, pharmacotherapeutics, toxicity and clinical trials are needed to provide sufficient data. In addition, research should be initiated for identification of elite chemotypes, quality control of produces through marker development such as TLC, HPTLC, standardization of cell culture techniques for production of bioactive compounds and identification of pathway related to the production of potent bioactive compounds. In order to realize these goals a number of projects have been initiated by academic institutions and pharmaceutical companies.

In nut shell, we can say that the combination of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology are needed to exploit the vast diversity of chemical structures and their biological activities for the development of new pharmacological agents. 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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