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Review Article
Published: 24 Aug, 2020

SF Journal of Clinical Pharmacology Research

Health Benefits of Plant-Derived Bioactive Secondary Metabolites as Dietary Constituents

Aryadeep Roychoudhury and Rituparna Bhowmik*

Department of Biotechnology, St. Xavier's College (Autonomous), 30, Mother Teresa Sarani, Kolkata, West Bengal, India

Abstract

Plants are one of the most important sources of human nutrition and they also act as store house of important pharmaceuticals. Plant-derived bioactive compounds have long been used to treat diseases in traditional medicine. Plant biotechnology provides a blooming opportunity for improving the bioactive compounds in our food. This coupled with the emergence of concepts like nutritional therapy and phytotherapy makes us curious about understanding the health benefits of the bioactive compounds in our food. Plant secondary metabolites have long played an important role as anti-inflammatory substances. Some functional metabolites help in curing chronic diseases, while phenolic compounds are well-known antioxidants which improve our overall heath. Long used in folk medicines, some bioactive compounds have antiviral, cardio-tonic and immune-stimulatory properties. Some again have a neuro-protective role, while some may even display anti-cancer properties. Coupling nutritional research with genomics may help us to improve our diet and prevent diseases. Use of animal models helps to study the immune responses to different plant-derived bioactive compounds, and the useful ones may be incorporated in our diet. This review addresses all the health benefits with special emphasis on immune-boosting ability of plant bioactive compounds in view of their role in nutritional therapy.

Keywords: Bioactive compounds; Plants; Health benefits; Secondary metabolites

Introduction

With the change in lifestyle due to ushering of industrialization, modern lifestyle-related diseases like diabetes and obesity crept in. For a long time, people tried to improve their health status by consuming more vegetables, fruits and other plant products to get sufficient bioactive secondary metabolites for maintenance of sound health. Today we are more drawn to remedial approaches like nutraceuticals, nutrition therapy or phototherapy, compared to chemical pharmaceuticals or radiotherapy [1-3]. With the growing market for herbal products and nutraceuticals, scientific studies and clinical tests on their effectivity are also on the rise. A number of plant biotechnological products have already been patented and their count is gradually increasing.

Nutraceuticals are generally supplements that provide the required amount of vitamins, lipids, minerals and other nutrients depending on their purpose [4,5]. Nutritional therapy is the upcoming trend of healing system which is based on the use of dietary therapeutics or nutraceuticals in place of chemically synthesised pharmaceuticals. This concept strongly believes in the medicinal potential of food in addition to its nutritional property. This makes use of several phytonutrients, which are plant-based bioactive compounds that are known to improve our health status. Several clinical trials have been conducted to investigate these bioactive compounds, one such study was carried out on 223 participants where oral nutritional supplementation was provided for acutely ill patients. They showed overall improvement in health status and a statistically significant reduction in number of health ailments [6]. Another study showed that consumption of large amount of grapes or grape products such as wine could contribute to low risk of chronic diseases, for example cardiac problems and even certain cancers [7].

In the event of the current coronavirus COVID-19 pandemic, some traditional herbal bioactive components and folk medicines could be implemented for their anti-viral activity. Some of these have proved to be successful against other human coronaviruses in Severe Acquired Respiratory Syndrome (SARS) and their addition to regular diet may boost our immune system. This review will give a comprehensive idea about several bioactive herbal remedies that help to improve our general health status, provide immunity and cure several diseases.

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*Correspondence:
Aryadeep Roychoudhury, Department of Biotechnology, St. Xavier's College (Autonomous), 30, Mother Teresa Sarani, Kolkata, West Bengal, India.
E-mail: aryadeep.rc@gmail.com

Received Date: 10 Jul 2020
Accepted Date: 13 Aug 2020
Published Date: 24 Aug 2020

Citation: Roychoudhury A, Bhowmik R. Health Benefits of Plant-Derived Bioactive Secondary Metabolites as Dietary Constituents. SF J Clin Pharm Res. 2020; 2(1): 1002.

Some Scientifically-Studied Nutraceuticals

The health benefits from grape extracts may be rooted down to the presence of bioactive polyphenols such as stilbenes and anthocyanins, condensed tannins like proanthocyanidins and some indole amines like melatonin and serotonin [7]. A popular nutraceutical Oligomericproanthocyanidins (OPC) patented by Professor Jacques Masquelier, has been marketed in western countries as a strong antioxidant and anti-ageing agent. It is a combination of bioactive secondary metabolites from grape seed, pine bark and red wine extract along with bilberry and citrus extract. Lipid peroxidation due to oxidative stress may lead to conditions like atherosclerosis, cardiovascular problems and even cancer. Bioactive extracts from soybean like isoflavone phytoestrogens, genistein and specially a daidzein metabolite, equol has strong antioxidant properties. It may even prevent oxidation of Low Density Lipoproteins (LDLs) in arterial intima [8,9]. Soy isoflavones may also mimic estrogen due to their structural similarity. An eight-week study conducted on thirty healthy post-menopausal women, where they were given 50 mg soy isoflavones projected increase in plasma nitrate and nitrite levels along with improved endothelium-independent vasodilation [10]. Studying the world statistics of breast cancer cases, with western countries having significantly higher number of cases, scientists established that vegetarian diets, rich in isoflavonoids, lignans and dietary fibres could be the causative factor for this difference. These bioactive compounds modulate the natural sex hormone balance in our body by exhibiting an estrogenic or anti-estrogenic competitive effect [11].

Another advantage of nutrition therapy over herbal pharmaceuticals, which contain a single secondary metabolite, is that these mixtures of bioactive components may act in synergistic manner targeting multiple cellular components, leading to a more holistic approach. Phytotherapy strategies that make use of a combination of herbal drugs is proven to be more effective than isolated herbal drug treatments [12]. One such multi-component herbal drug STW5, developed by Swedish scientists, has been clinically approved as an effective treatment for functional dyspepsia and irritable bowel syndrome [13]. The clinical efficacy of this multi-component herbal drug questions the current therapeutic strategies of targeting a single receptor group, without taking into consideration the other connected signalling networks. Studies of Hijikata et al. [14] reported the efficacy of a traditional Chinese herbal formulation Bu-yang-huan-wutang, against epileptic seizures. Decreased seizure frequency and intensity was observed in all three of the tested patients. It was believed that this treatment inhibited blood stagnation in cerebrovascular system, which is the underlying cause of several cerebral ailments [14]. Another clinically successful Chinese formulation Aller-7 is shown to be effective against allergic rhinitis [15].

Different Health Benefits of Food Bioactive Compounds

Anti-inflammatory and antioxidant compounds

Diseases like diabetes, cancer and photo-ageing can be attributed to inflammation as their causative agent or triggering factor. Inflammatory responses modify the transcriptome by upregulating several transcription factors and pro-inflammatory cytokines of our tissues, inhibits insulin signalling and even poses risks of cardiovascular ailments. A solution to unresolved inflammation could be plant bioactive compounds that exhibit natural anti-inflammatory activities, often in conjugation with antioxidant properties [16].

Kicel et al. [17] provided a detailed study based on the chemical composition of Cotoneaster fruits. This fruit from Poland is known for its range of polyphenolic components that are known for their health-promoting properties. Their bioactive secondary metabolites have been studied using chromatographic and spectroscopic methods, the most potent polyphenolic constituents were then subjected to analysis for antioxidant properties. They carried out eight *in vitro* tests with chemical and biological plasma models to detect if these hydrophilic or lipophilic polyphenols could scavenge free radicals, thereby enhancing the non-enzymatic antioxidant property of blood plasma and protecting the lipids and proteins from oxidative damage. These bioactive constituents from the nine species of Cotoneaster fruits also acted as potent inhibitors of pro-inflammatory enzymes like lipoxygenase and hyaluronidase. These fruits would find promising anti-inflammatory and antioxidant applications in pharmaceuticals and nutraceuticals. They may form a valuable part of a balanced diet in association with other bioactive compounds.

Another important bioactive compound known for anti-inflammatory property is polyacetylene. Carrot is a good source of polyacetylenes like Falcarinol (FA) and falcarindiol (FD) which acts by suppressing the Nuclear Factor (NF) κB. FD carries out S-alkylation of Kelch-like ECH-associated protein 1 (Keap1), thereby disrupting its inhibitory effect on Nrf2. Stefanson and Bakovic [18] studied the protective impact of FA against intestinal inflammation to establish that FA was a very potent inducer of Heme Oxygenase-1. It was in fact stronger anti-inflammatory agent in comparison to sulforaphane, a potent activator of Nuclear Factor Erythroid 2 (NFE)-related factor (Nrf2)/ Antioxidant Response Element (ARE) pathway. Diet achievable doses of FA was sufficiently potent in attenuating intestinal inflammation and could form a valuable constituent of balanced diet and herbal therapeutics.

There is an intricate balance between inflammation signalling and free radical redox reactions which when uncontrolled woks in a feedback loop. Under dire circumstances, this may even lead to organ dysfunction like sepsis. Naderi et al. [19] carried out their studies on *Morus nigra* L. (black mulberry) for its antioxidant properties, testing it on sepsis model induced by lipopolysaccharide (LPS). A group of male mice models was treated with 100 μL of mulberry extract for twenty one days, while another untreated group served as control, and then sepsis was induced. The mulberry extract appeared to be beneficial for these mice, as it modulated the important parameters that were usually altered in sepsis. While attempt to find a suitable treatment of sepsis was sought after for last few years, none of the remedies proved clinically beneficial. Lipid such as omega-9 fatty acid is a natural Peroxisome Proliferator-Activated Receptor (PPAR) agonist which can protect animals against sepsis. PPAR gamma ligands inhibit microvascular dysfunction and even enhances anti-bacterial properties through neutrophil extracellular trap formation. Isabel Matos Medeiros-de-Moraes et al. [20] demonstrated that olive oil, rich in omega-9 fatty acid can regulate corticosterone levels, inflammation signalling, cell motility, bacterial inhibition and nuclear receptor of PPAR gamma expression mainly in liver and adipose tissue. This bioactive lipid could decrease the levels of proinflammatory cytokines, increase interleukin (IL)-10 productions and in turn restrict neutrophil migration and improve antibacterial properties. Leukocyte trafficking in septic animals was also affected by omega-9 fatty acid, as it decreased selectin dependency of leukocyte rolling *in vivo*.

Neuroprotective compounds

Most of the neurological disorders such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, neuropathic pain, etc. can be traced back to neuro-inflammation. Both age-related conditions and age-independent pathologies could lead to neuro-inflammation *via* similar cascade. About two million people worldwide die of cerebral ischemic diseases every year. Some remedies for this condition come from herbal sources. The effect of total flavonoids was studied from *Abelmoschus esculentus* L. against Transient Cerebral Ischemia-Reperfusion Injury. It was suggested that the protective effects were due to direct or indirect antioxidant actions via free radical scavenging or activation of Nrf2-ARE pathway respectively. Oxidative damage plays an important role in neuronal damage [21], which may proceed to cause neurodegenerative diseases such as Alzheimer's. Pequi, a phytomedicine derived from *Caryocar brasiliense* of Caryocaraceae family, is known to be a potential neuroprotective medicine. de Oliveira et al. [22] reported the mechanism of this neuroprotective effect to be due to anti-cholinesterase or antioxidant properties. Some procyanidins, extracted from lotus seedpod, exhibited anti-Aβ effects in rat models. These extracts are promising phytomedicines against Alzheimer's disease. Studies show that cyclic AMP response element/brain derived neurotropic factor (CREB/BDNF) signalling pathway may be responsible for the antioxidant and neuroprotective effects of these procyanidins. Another potential candidate is resveratrol-enriched Dongjin rice which shows cytotoxic and anti-neuroinflammatory properties. Discovery that resveratrol-enriched rice inhibited the Mitogen-Activated Protein Kinase (MAPK)-NF-κB signaling pathway helped to elucidate the mechanism of action of resveratrol as anti-neuroinflammatory agent. The role of resveratrol against ageing is also established along with the potential of normal Dongjin rice due to its abundance of bioactive compounds such as α-tocopherol and γ-tocopherol [16].

Anti-cancer compounds

Today, several plant bioactive compounds are gaining importance as anti-cancer agents. Several studies also show that these natural components increase the efficacy of chemotherapy, and sometimes even reduce the side effects of chemotherapeutic drugs. Four such plant-based bioactive compounds namely curcumin, myricetin, geraniin and tocotrienols are well known for their anti-cancer properties [23].

Curcumin or Diferuloylmethane is derived from Southeast Asian plant *Curcuma longa* [24]. This plant is rich in curcuminoid compounds, which is a combination of several chemicals like curcumin, desmethoxycurcumin and bis-demethoxycurcumin. Natural curcumin has very low bioactivity; however, curcumin-derived compounds like E10, F10, FN1 and FN2 and its synthetic analogues are known to inhibit prostate, pancreas and colon cancer cells at concentrations lower than 1 μM [25,26]. It is also known to be effective against lung, pancreatic, melanoma, head and neck, breast, colorectal and ovarian cancers. It has diverse mode of actions such as inhibition of angiogenesis, proliferation and metastasis; it also decreases chronic inflammation and helps to immunize our body against mutant cancer cells. Carbocyclic curcumin analogue CUR3d, down-regulates phosphatidylinositol 3 kinase/ protein kinase B (PI3K/Akt) and blocks NF-κB pathway which makes it capable of inhibiting proliferation of liver cancer cells at concentrations of 100 μmol/L [27]. Higher concentrations of curcumin may also act on papillary thyroid cancer cells, inhibiting its metastasis.

Myricetin is a bioflavonoid, obtained from the bark of *Myrica nagi* Thunb [28]. It is well known for its activity against cardiac failure [29], diabetes [30,31] and cancer [32]. It acts as an anti-proliferative agent against liver cancer cells HepG2n [33] and T24 bladder cancer cells by halting these cells at G2/M junction and inhibiting cyclin B1 and cyclin-dependent kinase cdc2 [34]. Myricetin shows anti-cancer effects against ovarian, colon, skin, liver and breast cancers. This bioactive compound can also modulate B-cell lymphoma (Bcl)-4 family proteins, thereby inducing apoptosis in T24 cells [35]. A recent study also reports myricetin to have anti-metastatic activity against breast cancer cells as it downregulates the expression of Matrix Metalloprotease (MMP)-2 and MMP-9 [36].

Geraniin is the main bioactive compound of many medicinal plants such as *Geranium thunbergii*. It possesses high antioxidant, anti-microbial, anti-diabetic, antiviral and anticancer properties. This compound mainly exists as hydrolysed products in the form of gallic acid, corilagin and ellagic acid. Geraniin is known to prevent breast cancer cell proliferation at half Inhibitory Concentration (IC50) value of 13.2 μg/mL [37]. *Phyllanthus urinaria* L. extracts rich in geraniin is known to prevent proliferation and cause apoptosis of Michigan Cancer Foundation-7 (MCF-7) cells. Studies on geraniin showed that it can prevent metastasis of lung cancer cells. Experiments on this bioactive compound indicates that it inhibits Transformation Growth Factor beta 1 (TGF-β1) induced epithelial to mesenchymal cell transformation in lung cancer cells by increasing E-cadherin expression and inhibiting the crucial transcription factor snail, leading to its anti-metastatic effect [38].

A major class of vitamin E, tocotrienol is also known for its anti-cancer properties. It is present in plant products like rice-bran oil, palm kernel oil, etc [39]. Both *in-vitro* cell based studies and *in-vivo* animal model experiments proved that tocotrienol exhibits anti-tumour properties and prevents proliferation of cancer cell lines such as pancreatic, liver, stomach, lung and breast cancers. Its anti-angiogenic and anti-proliferative properties result from its modulation of NF-κB signalling *via* Notch1 pathway [40]. Some reports also suggest that it reduces the levels of Vascular Endothelial Growth Factor (VEGF) and IL-8 in serum, which plays a major role in tumorigenesis [41]. While many other natural anti-cancer compounds are being discovered today, their mode of action and efficacy are still unknown. Hence, further studies in this field may someday help to replace the established chemotherapeutic methods by phytotherapy.

Anti-Viral Effects of Plant Bioactive Compounds

Bioactive herbal extracts have been used for treating diseases since ancient times, including viral infections. In the current situation of 2020 COVID-19 pandemic, we may fall back upon some of these plant-based bioactive secondary metabolites as anti-viral agents. COVID-19 like other coronaviruses belongs to the Coronaviridae family. Human coronavirus like COVID-19 Severe Acute Respiratory Syndrome (SARS) coronavirus [42] and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are known to cause common cold, mainly affecting the respiratory tract, which without a vaccine may sometimes prove to be fatal [43]. Naturally occurring terpenoid glycosides like saikosaponins (A, B2, C and D) found in *Bupleurum* spp., *Heteromorpha* spp., and *Scrophularia scorodonia* are known for their antiviral activity against one of the human coronavirus HCoV-229E [44]. These bioactive secondary metabolites were able to prevent

early stages of the viral life cycle such as attachment and penetration, thus helping to alleviate the disease symptoms. Bioactive compounds like myricetin, scutellarein and phenolic compounds from *Isatis indigotica* and *Torreya nucifera* are also reputed for their inhibitory action against SARS coronavirus enzymes such as nsP13 helicase and 3CL protease [45-47]. Another 3CL protease inhibitor effective against SARS coronavirus was obtained from *Houttuynia cordata*; this blocked the RNA-dependent RNA polymerase activity crucial for coronavirus survival [21].

Some of the indigenous herbs with proven anti-viral activity may help in a general way to boost up our immunity against the COVID-19 virus. They are:

(i) Oregano-Carvacrol is a bioactive secondary metabolite present in oregano that has proven antiviral activity against Murine Norovirus (MNV). Both pure carvacerol extracts and oregano oil have also proven effective against Herpes Simplex Virus type 1 (HSV-1), rotavirus and Respiratory Syncytial Virus (RSV). Thus, its inclusion in regular diet may prove beneficial [48].

(ii) Sage-Another member of the mint family like oregano, *viz*., sage (*Salvia officinalis*) has been used in traditional medicines for its antiviral activity since ages. This activity may be attributed to the bioactive component safficinolide present in its leaves and stem [49]. Sage extract is effective against deadly viruses like Human Immunodeficiency Virus type 1 (HIV-1) and HSV-1. It is also known to inhibit animal viruses like Indiana vesiculovirus.

(iii) Basil-Both sweet and holy basil extracts have bioactive compounds like apigenin and ursolic acid that act as potent anti-viral agents against herpes virus, hepatitis B virus and enterovirus. A four-week study, where 300 mg of holy basil extract was added to regular diet resulted in increased helper T cell and natural killer cell counts. Thus, this common folk remedy, holy basil or tulsi has scientifically proven immune boosting ability [50].

(iv) Fennel-Essential oil from fennel is rich in trans-anethole, a strong anti-viral agent effective against HSV-1 and parainfluenza type-3 (PI-3) virus. It is well known for its immune boosting and anti-inflammatory effects in combating viral infections.

(v) Garlic-Garlic, a common kitchen spice, is a potent natural remedy for wide range of conditions such as Human Papillomavirus (HPV) warts, influenza A and B, HIV, HSV-1, viral pneumonia, etc [51]. Regular garlic intake may help to boost immune system against several such viruses.

(vi) *Echinacea*-Several varieties of *Echinacea*, such as *E. pallida, E. angustifolia*, and *E. purpurea* are used as medicinal herbs. They have strong antiviral effects against herpes and influenza virus and may also help to strengthen our immune system against coronavirus [52].

(vii) *Sambucus*-Elderberries have been used in variety of natural elixirs and pills. Concentrated elderberry juice is known to suppress influenza virus replication [53]. Elderberry supplementation in regular diet may substantially reduce upper respiratory tract problems caused by viruses like COVID-19.

(viii) *Astragalus*-Astragalus Polysaccharide (APS) present in popular flowering Chinese herb *Astragalus*, exhibits anti-viral potential. In addition to their anti-viral effect against herpes viruses, hepatitis C, and avian influenza H9 virus, this bioactive compound protects human astrocyte cells of central nervous system in herpes [54].

Similar natural extracts and tinctures from several other herbs like essential oils from lemon balm exhibiting antiviral property against avian influenza (bird flu), herpes viruses, HIV-1, and enterovirus 71; bioactive components such as menthol and rosmarinic acid from peppermint acting as antiviral and anti-inflammatory agents; antiviral compounds like glycyrrhizin, liquiritigenin and glabridin present in licorice which even proved effective against SARS coronavirus; gingerols and zingerone from ginger that inhibit viral replication; oleanolic acid from rosemary which prevent viral infections, etc. may altogether act as general protectants against viruses [55]. However, most of these extracts and pure components have been tested *in vitro* and animal models using concentrated extracts. Their mode of action and medicinal impact on humans is rather obscure [55].

Conclusion

The aforementioned scientific studies and clinical trials clearly suggest that bioactive traditional herbs can prove to be highly effective means of disease treatment, often better than the chemical therapeutic options. However, the mechanism of action and most of the targets in synergistic pathway are still unknown which may hamper the commercial market of these products [12]. Standardization of plant extracts may help in implementing herbal drugs as in treatment of diseases in a similar way that chemotherapeutics has been used in the past. On the other hand, scientists also speculated negative effects of some diets to derive a more holistic understanding. Consumption of food rich in fat is directly related to increase in endothelial activation in men. This devastating effect is mainly attributed to large proportion of fatty acid content of the diet [56]. Higher intake of trans-fat is also associated with higher risk of cardiovascular problems, which is indicated by the adverse effect on lipid profile and endothelial function [57-59]. Mozaffarina et al. [57] in their studies established a relationship between trans-fatty acid and increased risk of coronary arterial diseases and diabetes in women. Intake of dietary fatty acid could also be related to higher tumour necrosis factor α-receptor concentrations and higher interleukin 6 and C-reactive protein concentrations in women [57].

Even though some of these concerns exist, government, scientists and nutritionists are trying to widen the use of nutritional therapy. Advancements made in plant biotechnology such as micro-propagation and genetic engineering as well as techniques to diagnose and standardize the bioactive compounds widen the horizon for this field. Techniques such as cDNA microarray can serve to diagnose wild plant species for medicinal components. DNA fingerprinting and epigenetic studies may someday make it possible to study the entire genetic background of an unknown herb and predict its nutrition potential. Such information may come handy to professionals such as nutritionists to suggest suitable dietary supplements for each individual, depending on their health status [60]. Metabolic screening of newborns makes it possible to know beforehand the kind of diseases they may suffer from, following which they may be treated with specific nutritional therapy or phytotherapy, based on their conditions [61]. In the present scenario of COVID-19 pandemic, inclusion of antiviral bioactive supplements in our regular diet is more of a necessity rather than choice. It could help to boost our immune responses even against newer viruses that may emerge in future. Sooner or later we will welcome most of these nutraceuticals into our regular life, and hopefully these effective plant products with lesser side effects will serve as a better alternative to the stereotyped medicines and antibiotics.

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