Chapter

PHYTOCHEMICAL DEFLECTION OF HARMFUL INFLAMMATORY EVENTS TOWARD MORE EFFECTIVE IMMUNE ACTIVITY

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ABSTRACT

A large number of disorders are associated with two changes in immune reactivity. Firstly, a flourishing disease is often accompanied by depression of effective immune surveillance. This shortcoming allows both invasive microorganisms to proliferate and also leads to survival of abnormal cell types, some of which may proliferate and become transformed to malignant variants. A second feature common to several chronic disease states, is the development of ineffective immune

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reactions, largely typified by elevation of non-selective generalized inflammatory events. Both of these characteristics adversely affect control and limitation of disease progression. These deficits comprising ever evolving levels of inflammation and a poverty of beneficial immune responses, are also found in normal aging and consequently are especially marked in age-related ailments.

The basis for the use of micronutrient phytochemicals is to optimize health in normal subjects and thus pre-emptively assure that the response to an adverse disease event will be the best possible. The maintenance of a high level of fitness in advance of untoward circumstances, is important in delaying and limiting the consequences of both disease states and changes accompanying senescence.

This report emphasizes the utility of a series of micronutrient phytochemicals that are able to redirect immune responses toward a more specific goal, while diminishing the propensity of inflammatory mechanisms to be over-reactive and inappropriately directed. In general, phytonutrients tend to be less directed toward a single metabolic site than are pharmacological agents, and tend to impact a series of targets. While they are not essential like vitamins and essential minerals, they are likely to have substantial benefits regarding overall human health and longevity as a result of their disease-preventing properties. This breadth of action and generally low toxicity is in contrast to pharmaceuticals which carry a higher risk of adverse side effects. This makes phytochemicals eminently suitable for extended usage over a prolonged period.

INTRODUCTION

Natural products have been used for both health maintenance and for medicinal purposes for several millennia. In the last 150 years they have been increasingly displaced by more purified preparations generally made by procedures common to organic chemistry. These man-made chemicals have the virtue of being free of unwanted contaminants and of generally having greater potency. They can also target a precise molecular event and can thus have a more focused site of action. Pharmacological drugs are normally used in response to the appearance of a distinct disease, the aim being to restore health and well-being by pinpointing the site of impairment and using a selected chemical to target that site. This focal approach is especially useful in cases of an acute injury incurred by an exogenous infection or an endogenous metabolic disturbance with a

circumscribed perimeter. New drugs are constantly developed and synthesized, designed to increase the specificity of their actions, and minimize adverse side effects.

The limitations of synthetic drugs are often inherently to be found in the very features that constitute their strengths. Thus, the potency and narrow site of action of such agents can lead to robust metabolic compensatory responses intended to restore cellular homeostasis.

While many drugs are effective in the short term, this tendency of the body to restore equilibrium when metabolism is driven in a novel direction can result in reduced efficacy of action after prolonged application of a drug. The development of such refractory resistance is often combined with the emergence of undesirable side effects. Such effects can be seen in the case of drugs used to treat many chronic conditions such as asthma, Parkinson's disease and schizophrenia, all of which require repeated application of medication. The re-emergence of the underlying condition in time, is often combined with the onset of unwelcome sequelae. Drug resistance is an ongoing problem and is one of the drivers in the continual search for products.

Recently the usefulness of corticosteroids in treating COVID-19 has been brought into question. While reducing mortality on extreme cases, in other situations, this powerful suppressant of immune responses can prolong the survival of the virus in the body (Mudd et al., 2020, Russell et al., 2020). In contrast, the perceived shortcomings of natural products, their lack of specificity, their lower potency, and their often containing a range of related molecular species rather than a single chemical, can also lead to the advent of distinct benefits. All of these features tend to interrupt an undesirable sequence of intracellular changes or promote a beneficial trajectory is a more diffuse manner. A metabolic chain of events is likely impacted on at several sites, which reduces the likelihood of occurrence of a countervailing attempt to reverse effects. Melatonin has been found to be of value in treatment of COVID-19 without appearing to possess the limitations of steroids (Zhou et al., 2019). The generally broader but less intense impact of natural products also allows their use for more extended time periods. Thus, while application of strong pharmacological agents is

most suitable for acute situations, whether relating to pain, infection, injury or some form of organ collapse, natural products may be most useful in treatment of chronic disease or in continued maintenance of optimal health through the lifespan.

It is known that the immune system grows less effective with aging and trends toward generation of non-targeted inflammatory changes. This is the major reason for the large increase in mortality in the elderly relative to the young, attributable to COVID-19 infection. This increasing susceptibility to poor immune reactions is a rationale for proposing augmenting the immune response in the aged by the continuing use phytonutrients. This recommendation is not confined to the ailing but also to the health aging population. In contrast to many pharmacological agents, the agents discussed are all well tolerated and suitable for extended use, and have minimal untoward side effects. Furthermore, there is little evidence of the development of metabolic reaction designed to maintain homeostasis by reversing the more restrained effects of these products.

Some general comments apply to nutrient phytochemicals as a whole:

1. Most of the agents to be discussed act by regulation of uncontrolled inflammatory processes and free radical generating oxidant events that typify many chronic disease states and well as senescence (Bondy and Sharman, 2010).
2. It has been difficult to link specific health benefits to specific phytochemicals. The complex nature of these chemicals within plants, and the common heterogeneity of each class of compound, has made epidemiological validation of benefits challenging.
3. Due to the many sites of action often found to be affected by a single phytochemical, pinpointing their precise mechanism of action has also been problematical. Very few studies in the literature compare different phytochemicals so it is difficult to know whether as given agent has a distinctive target of whether many of these agents in fact, act at the same sites.

4. The valuable attributes of these agents are generally not apparent immediately but may take an extended period to become manifest. This further confounds evaluation of their value.
5. Despite all these handicaps to assessment of the utility of phytochemicals, there is broad epidemiological evidence derived from distinct populations, of the health value of a predominantly plant-based diet (Medina-Remón et al., 2018).

Some classes of phytochemical and other biological agents are briefly discussed but rather than primarily stressing the literature on effects of individual compounds, this review addresses the question of those major intracellular processes where phytonutrients might act in a supportive manner. The emphasis of this review is in suggesting that many phytochemicals have a broad resemblance in their key sites of action. If this is the case, more attention needs to be given to their degree of access to intracellular compartments and to the kinetics of their persistence. The sections are thus subdivided so as to center on analysis of the crucial biological events that lead to improved cellular health and effectiveness.

KEY BIOLOGICAL PROCESSES THAT CAN BE MODULATED BY PHYTONUTRIENTS

There are some key networks that have a major impact on the qualitative and quantitative nature of immune responses.

1. *Activity Level of Inflammation-Related Genes*. These include pathways containing transcription factors such as NF-kB involved in activating genes related to both the innate and adaptive immune response systems. This includes enhancement of production of mRNAs for inflammatory cytokines which are widely implicated in many inflammatory diseases.

2. *Expression of antioxidant, anti-inflammatory and detoxification genes.* In contrast other networks support production of antioxidant and anti-inflammatory processes. A premier example of this is the Keap1-Nrf2-antioxidant element response (ARE) pathway. The Keap zinc finger protein binds to the Nrf2 transcription factor and this binding is loosened under condition of oxidative stress, allowing Nrf2 translocation to the nucleus. This allows derepression of DNA sites containing the antioxidant response element and consequent expression of a series of antioxidant and cytoprotective proteins.
3. *Histone deacetylation of sites allowing increased expression of mRNAs supporting cell survival.* Sirtuins are another group of NAD+ activated signaling proteins, several of which can deacetylate nuclear histones and thus weakening their binding to DNA. SIRT1 activity requires NAD+ and enhancing the concentration of this can enhance SIRT1 effectiveness (Xie et al., 2020).

   Sirtuin-1 (SIRT1) levels are elevated in response to various stressors and toxicants including inflammatory and free radical producing events. This enables increased expression of proteins including endocrine factors which promote cell survival. Activation of this suite of genes may be protective against neurodegeneration, vascular inflammation and excessive storage of lipids. However, SIRT1 can have both pro- and anti-inflammatory effects of differing cell types (Chadha et al., 2019).
4. *The mammalian target of rapamycin complex1 (mTORC1) signaling pathway.* This pathway activates a series of kinases and integrates upstream metabolic and energy-related events (LaPlante and Sabatini, 2009). It also down-regulates immune responses. Inhibition of this pathway by rapamycin and its analogs may be beneficial for a range of neurological disorders, cancer and may also slow the onset of age-related changes (Johnson et al., 2013).

TYPES OF PHYTOCHEMICAL WITH PHARMACOLOGICAL POTENTIAL

The compounds are listed, initially with emphasis on their utility to the organisms synthesizing them. Insufficient consideration had been given to the original evolutionary purpose of these chemicals but such information may help to illuminate the mechanisms underlying their potential clinical applicability. Less emphasis is given to the applications of agents for treatment of human disorders as claims are often very broad and generally encompass a large range of diseases. In view of this, the issue of whether compounds act at very similar loci or have the potential to interact in a synergistic manner is relevant and largely unexplored.

Polyphenols

Polyphenols generally promote SIRT1 and Nrf2/ARE activity and inhibit pro-inflammatory events by reducing NF-kB activity (Sarubbo et al., 2018).

Flavonoids such as quercetin consist of a 15-carbon frame consisting of two phenyl rings and a heterocyclic ring. Quercetin is a plant pigment present in onions, grapes, berries, broccoli, and citrus fruits. It can protect plants against oxidative stress in the presence of free-radical generating agents such as paraquat (Zerin et al., 2013). The neuroprotective effects of flavonoids have been attributed to enhancement of Nrf2/ARE and SIRT1 together with inhibition of NF-kB (Dong et al., 2017, Velagapudi et al., 2018).

Resveratrol and Pterostilbene (trans-3,5-dimethoxy-4-hydro xystilbene) are stilbenoid polyphenols, where two phenol rings linked to each other by an ethylene bridge. Pterostilbene and resveratrol are major antioxidant component of grapes, blueberries and peanuts, produced in greater amounts in response to tissue damage and invasive organisms. These agents may predominantly but not exclusively act on the sirtuin

class of NAD(+)-dependent deacetylases, (Kane et al.,) and are considered a promising new strategy in treatment of many diseases involving oxidant and inflammatory processes, especially those relating to senescence (Sarubbo et al., 2018). One of the beneficial systems by resveratrol is the Nrf2/ARE trajectory (Kim et al., 2018).

Curcumin is a polyphenol made by the *Curcuma longa* plant with anti-oxidant and anti-inflammatory properties. It is of value to the plant because of its antimicrobial and antifungal properties and its ability to repel various insect species. It is currently being tested in several clinical trials as an adjunct therapy for various forms of cancer (Tomeh et al.,2019). Nrf2/ARE is a key pathway activated by curcumin (Jiang et al., 2020).

Epigallocatechin gallate is a polyphenolic ester found in teas, fruits and dark chocolate. In plants, it is protective against fungi such as *Botrytis cinereal* and can block seed germination under adverse environmental conditions. Both epigallocatechin and resveratrol enhance the Nrf2/ARE track and this may lead to carcinostatic effects in several organs (Smith et al., 2016).

Anthocyanins are brightly pigmented water-soluble diacid flavonoids found in blueberries, raspberries, black rice and many other blue or purple vegetables. They play a role attracting the pollinators and seed dispersers essential for plant reproduction. By virtue of their direct anti-oxidant properties and ability to activate the Nrf2 pathway they are protective against high light stress and their coloration can also serve as a signal to discourage herbivory. Their antioxidant properties maty also account for the attributed value of plants high in anthocyanins in the mitigation of cardiovascular disease (Blesso, 2019).

Isoflavones such as genistein are flavonoid polyphenols found especially in soybeans. Their usefulness to plants is that they induce nodulation in plant-growth promoting rhizobacteria that reside on the roots of the plant (Mabood et al., 2006). These bacteria confer systemic resistance of the plant against the destructive bacterium *Xanthomonas axonopodis pv. Glycines.* As well as stimulation of the Nrf2/ARE pathway (Liang et al., 2018), isoflavones bind to estrogen receptors and possess both weak estrogenic and anti-estrogenic activity. They have low solubility

in water and have a bitter taste. The anti-estrogenic properties of isoflavones may reduce the risk of hormone-associated cancers (breast, uterine, and prostate), while estrogenic effects in other tissues may promote maintenance of bone mineral density and lowering of LDL- and raising of HDL- cholesterol. An association has also been suggested between soybean consumption and improved cognition (Cui et al., 2020). On the other hand, low level disruption of estrogenic events may also have undesirable effects (as is shown in the case of bisphenol A) and thus use of this class of agent may thus have negative consequences (Patisaul et al., 2017).

Berberine is a yellow alkaloid polyphenol isoquinoline with a tetracyclic skeleton. It is found in many plants where its value is probably due to its anti-microbial activity. In addition to claims of its utility as an anti-oxidant and anti-inflammatory agent and activator of the Nrf2/ARE system (Ashrafizadeh et al., 2020), it has found more specific use in the treatment of cancer and diabetes. It has been reported as effective as metformin in the treatment of mild Type 2 diabetes. Several reports of berberine toxicity exist (Martini et al., 2020) and thus this agent is potentially more hazardous than most of the others agents discussed.

Organosulfur Compounds

The biological utility of these agents in both the plants that manufacture them and the animals that consume them is thought to be due to redox-reaction with -SH groups in glutathione and proteins, thus preserving intracellular reducing power.

Sulforaphane is an organic isothionate material synthesized in response to injury by cruciferous vegetables including broccoli, cauliflower, Brussels sprouts, cabbage, mustard greens, and watercress. Its promotion of the Nrf2/ARE sequence is a major means of supporting anti-inflammatory events (Calabrese et al., 2020). It has anti-inflammatory and anti-oxidant properties.

Allicin is an organosulfur compound obtained from garlic. It is produced from the amino acid, S-allyl cysteine sulfoxide upon tissue damage to the plant. Allicin can either kill or inhibit proliferation of a range of invasive bacteria and fungi (Müller et al., 2016). Its reducing properties may account for this and for its ability to alter immune cell signaling but allicin has a range of poorly understood properties (Borlinghaus et al., 2014).

Carotenoids

Lycopene is a red carotenoid antioxidant found in some red fruits and vegetables including tomatoes, carrots, and watermelons. Its utility to plants may relate to ultraviolet protection during photosynthesis in sunlight. It has no β-carotene vitamin activity but is able to enhance the Nrf2/ARE pathway and the act as an antioxidant (Inoue et al., 2017a). *Lutein* is a related compound with analogous features.

Ginkgolides

Ginkgolides are diterpenoid lactones found in *Ginkgo biloba*, with 20-carbon structures arranged in six 5-membered rings. These compounds are effective in repelling insect predators from the plant and also inhibit larval detoxifying enzymes including glutathione transferase, acetylcholinesterase, carboxylesterase and mixed function oxidase (Pszczolkowski et al., 2011, Pan et al., 2016). These combined qualities provide the plants with significant protection from insects.

Extracts of *Ginkgo biloba* extract has been used medicinally for over 1000 years for its neuroprotective, anti-cancer, cardioprotective, and stress alleviating properties. In addition to its antioxidant and anti-inflammatory nature enable by activation of the Nrf2 pathway (Liu et al., 2019), its beneficial qualities have been attributed to its specific inhibition of platelet activation factor (PAF) which is involved blood coagulation and the

furthering of inflammation. Ginkgo extract and other PAF inhibitors can block the excessive and undesirable immune activity found in allergies and asthma and other types of inflammation (Gerstmeier et al., 2019). Inhibition of PAF has been found to block the aggregation of β-amyloid peptide and ginkgolides have been found useful in the treatment of Alzheimer's disease and cerebrovascular disease (Mango et al., 2016, Liao et al., 2020).

Omega-3 Fatty Acids

These essential polyunsaturated fatty acids are found in many plant and marine oils and characterized by the presence of a double bond three atoms away from their terminal methyl group. Eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are found in fatty fish and other marine organisms while α-linoleic acid is found in a range of nuts and seeds. They are important constituents of cell membranes and also act as activators of several receptors involved in signal transduction. These signaling events tend to reduce inflammatory activity and promote glucose uptake by cells. It is likely that omega-3 fatty acids perform these functions in plants and animals. In addition, as they have a lower freezing point than most lipids, their high content in cold water fish is advantageous in maintaining membrane fluidity at temperatures near freezing. Fish are not able to synthesize omega-3 fatty acids and obtain them from single celled phytoplankton, often by way of the food chain, initially being transferred to zooplankton (De Carvalho et al., 2018).

The use of these lipids has been reported to be beneficial in the treatment of a range of disorders including cardiovascular disease, various forms of dementia and rheumatoid arthritis. Both the SIRT1 and the Nrf2 trajectories are stimulated by these compounds (Inoue et al. 2017b, Zhang et al., 2014).

f. Melatonin

This is a pleiotropic hormone predominantly released by the pineal in animals, and functions in the diurnal light-dark cycle and in both animals and plants, acting as a potent hormone and immunomodulator (Agathokleous et al., 2019). Melatonin is also made in plants where it can play many roles including regulation of development, seed germination, and fruit ripening. In plants, melatonin can also mount effective immune responses and defenses against many kinds of stressor including drought, extreme temperatures, excessive salinity, and anthropogenic pollution. The widespread occurrence of melatonin among several phyla indicates its early evolutionary origin and its importance. Its oft-reported antioxidant properties are likely to be indirect and mediated by amplifying signaling pathways, as it is not present within cells in sufficient amounts to be a direct anti-oxidant and effective scavenger of free radicals. It is synthesized from tryptophan by both animal and plant species.

Administration of exogenous melatonin has been reported to lead to a broad series of health improvements (Bondy, 2018, Ferlazzo et al., 2020). Rather than inhibiting immune responses, melatonin appears to modulate them in a beneficial direction (Hardeland, 2019, Bondy and Campbell, 2020). A major contention that has been made for melatonin is related to its apparent ability to slow down the normal rate of senescence, most likely at the level of alteration of gene expression (Sharman et al, 2007). A variety of positive outcomes may secondarily emerge from such retardation, such as a reduction of the incidence of age-related disorders including neurodegenerative disease and cancer (Sharman et al., 2011).

THE ALTERATION OF REGULATORY PATHWAYS BY PHYTONUTRIENTS

Phytonutrients can effect substantial regulatory changes in each of the major sequences described above. Table 1 summarizes the many reports of positive effects of various phytochemicals on either inhibition or

promotion of these pathways. What is rather remarkable is the degree of overlap between various active agents in their reported sites of action. In addition, each phytonutrient considered individually has considerable breadth of sites of action that are affected.

The antioxidant and anti-inflammatory sequence of events enabled after activation of the Nrf2/ARE pathway is generally helpful in mitigating the effects of many chronic inflammatory states (Ahmed et al., 2017). Similarly promotion of SIRT1 generally leads to improved outcomes. Several phytochemicals that may be helpful in treatment of Alzheimer's disease, act by reducing activity of the NF-κB inflammatory pathway by inhibition of the degradation of IκB and of translocation of NF-κB to the (Seo et al., 2018). However, while suppression of extended NF-kB inflammatory activity is desirable in persistent inflammatory disease, action of this transcription factor is important in integrating an acute inflammatory response to the presence of abnormal cells or exogenous organisms, thus bringing about their elimination.

Table 1. Positive or negative effect of various plant-derived chemicals on key routes by which inflammatory and pro-oxidant events are regulated

Phytochemical	mTOR inhibited	NF-kB inhibited	Nrf2/ARE activated	SIRT-1 activated
Resveratrol/pterostilbene	+and -	+	+	+
Curcumin	+	+	+	+
Epigallocatechin		+	+	+
Quercetin	+	+	+	+
Sulforaphane	-	+	+	+
Allicin	+	+	+	+
Anthocyanins	+	+	0	+
Melatonin	-	+	+	+
Lycopene	+	+	+	+
Ginkgolides	-	+		+
Berberine	+	+	+	0
Isoflavones	+	+	+	+
Omega-3 fatty acids	+	+	+	+

The consequences of inhibition of the mechanistic target of rapamycin (mTOR), a serine/threonine kinase, are equivocal. Its excess content in tissues is associated with several persistent pathological conditions where age is a key factor, including cancer, neurodegenerative disease, arthritis and diabetes. mTORC1, a component of the mTOR complex, drives the expansion of immune T cells and thus promotes inflammation (Perl, 2015). A variety of plant materials depress levels of mTOR and have thus been linked to cancer prevention and improved outcomes of cancer treatment (Badar et al., Naujokat et al., 2020). The powerful immunosuppressant properties of mTOR inhibitors has made then useful in organ transplantation. While their use has been advocated for improving longevity (Blagosklonny, 2019), it should be borne in mind that mTOR signaling has an important integrative function in the regulation of growth, development and cellular energy regulation and its inhibition can lead to toxic consequences (Zhang et al., 2019). Such side-effects are less likely with the phytochemicals listed than with bacterially derived rapamycin which targets mTOR with great specificity.

The mechanisms by which these broad regulatory pathways are affected by phytochemicals is likely to involve several other factors not discussed. These include affecting the expression of microRNAs (McCubrey et al., 2017). For example, treatment with curcumin decreases the expression of miR-21 and miR-34a, while the tumor suppressor let-7a miRNA is upregulated (Mudduluru et al., 2011, Subramanian et al., 2012). Also, modulation of the gut microbiome by phytochemicals is likely to be an important contributor to their health promoting qualities (Blesso, 2019).

LIMITATIONS OF PHYTOCHEMICALS

Bioavailablity

The extent of the bioavailabilty of many of the compounds described is a major problem since they often have very limited solubility in water. Many solutions to this are being studied including the use of nanoparticles,

liposomes, emulsions and lipid carriers (Del Prado-Audelo et al., 2019, Ojalide and Sakar, 2020).

Another feature potentially limiting utility is the rate of metabolism of compounds, if this is very rapid, their utility can be limited. The short half-life is intracellular quercetin exemplifies this (Iside et al., 2020) where bioavailability is only around 2% of an oral dose (Costa 2016), while sulforaphane has been reported to be more stable than most phytochemicals (Konrad and Nieman, 2015, Houghton, 2019). Finally, some phytochemicals such as quercetin bind to plasma proteins and this can limit their transfer into cells (Li et al., 2016)

Potential Toxicity of Phytochemicals

The ingestion of large amounts of antioxidant chemicals such as vitamins, lipoic acid and acetyl cysteine can alter redox levels within the cell. This can be beneficial but excessive use of such chemicals can lead to an excess of reducing elements, which nan have adverse effects. (Narasimhan and Rajasekaran, 2015). This imbalance, reductive stress, is unlikely to be caused by most phytochemicals since they do not act directly as antioxidants but rather work by modulation of metabolic signaling pathways (Lee et al., 2014).

The applicability of agents to a specific disorder is not always well understood and this can pose a hazard. For example, activity of the Keap1/Nrf2 pathway leading to derepression of the ARE pathway, is generally beneficial but may be harmful if administered to patients with advanced cancer (Malavolta et al., 2018). Overactivation of this system is associated with drug-resistant cancer, cardiac hypertrophy (Smith et al., 2016). In general, benefits appear to outweigh risks in enabling this pathway, even in many cases of cancer (Qin and Hou, 2016).

Lack of Standardization of Phytochemicals in US Market

The purity and content of phytochemical products are not strongly regulated in the USA, unlike Germany, and this results in great heterogeneity in the composition of commercially available products. Many phytochemicals are marketed as complex and probably inconsistent mixtures.

Large variances have been found in the pharmaceutical quality of ginkgo extracts where differences include outright adulteration, toxic contaminants, and solubility (Kressman et al., 2002). These could contribute to the variable toxicity of ginkgo preparations. Furthermore, phytochemicals like most drugs have a biphasic benefit curve and can be toxic under some circumstances (Mei et al., 2017). Such concerns of purity and undesirable side effects can limit the utility of plant preparations. Epidemiological studies are already subject to a range of confounders and are further handicapped by such issues. Thus, attempted associations of herbal and supplements with cancer risk, involving careful study of large populations (Satia et al., 2009), can yield suggestions of both beneficial and harmful effects but can never be really definitive.

Lack of Detailed Mechanistic and Clinical Research on Natural Products

There is a paucity of valid mechanistic and clinical research that has been conducted on phytochemicals. This may to some degree be attributable to their prevalence; the consequent difficulty of patenting individual products leading to reduced commercial interest. Unfortunately, this leaves the consumer without authoritative scientific advice concerning the utility, or dosage of the host of products available. This is in stark contrast to the detailed instructions and warnings accompanying chemically manufactured pharmaceutical products.

Uniqueness of Each Phytochemical

The effectiveness of each of these compounds has been described as impinging on numerous other targets within the cell. This makes actual number of primary targets of a specific phytochemical very difficult to ascertain. The degree of correspondence between their properties and the distinctive qualities of each agent cannot be determined without more rigorous investigation. A recent example of the complexity of this issue is the emergence of cannabidiol as a phytochemical with potential value for a wide range of ailments including schizophrenia, epilepsy, chronic pain and Parkinson's disease. While a major site of action of CBD is obviously on cannabinoid receptors, around 20 other potential sites of action have been described (Eisenstein, 2019). Thus, a single pure phytochemical is likely to have many targets within the cell.

The selection of endpoints for study differs with each group of investigators. Many claims have been made for the selective value of a given phytochemical product in treatment of a specific disease. However, until phytochemicals are tested by a standardized uniform protocol, true comparisons cannot be made.

CONCLUSION

All four of the pathways selected for this report can under the appropriate circumstances, have both positive or adverse effects on overall wellbeing. Thus NF-kB activity is important in mounting effective immune responses to invasive bacteria and viruses, while SIRT1 has been shown to be either a tumor activator or a tumor suppressor under differing experimental conditions. mTORC1 has an indispensable role in development its continuing activity after the transition from maturation to aging appears to promote development of a range of age-related disorders. A robust Keap1-Nrf2-ARE signaling system is known to have many positive aspects but its overactivity can lead to multi-drug resistant cancer and cardiac myopathy by inducing 'reductive stress' (Narasimhan and

Rajasekaran, 2015). Phytochemicals by virtue of their non-selective targeting of a wide range of sites and their relatively low potency may be less likely to promote the appearance of such adverse events. They are more suitable for extended low level consumption that are more focused and more potent synthetic drugs. These differences also reduce the likelihood of plant derived agents causing major undesirable side effects. However, it is still important to purify such products so that they can be well-defined and characterized, rather than relying on crude botanical extracts with a range of bioactive components.

There seems to be major overlap between the effects of phytonutrients on several key metabolic signaling pathways. In view of this apparent similarity, it may be asked whether a very limited selection of the large range of these phytonutrients can suffice to produce optimal health benefits. The use of several phytochemicals in combination appears to be more effective than a high dose of a single component (Konrad and Neiman, 2015). In future it will be necessary be to define that blend of phytochemicals that together will lead to the most favorable health effects, and thus to create a rational formulation for their optimal admixture. Only with this knowledge can a blend be developed whose components act positively and in a synergistic manner.

Protracted low level therapies need to be found for dealing with the ever-increasing incidence of neurodegenerative disease prevalent in an aging population. The use of non-harsh preparations of plant origin to reduce neuroinflammation is likely to be helpful in this regard (Bondy et al., 2020). In view of their commonality in nature and likelihood of human consumption of several active phytochemical agents for many millennia, it is also more likely that their ingestion is less metabolically disturbing than that of recently synthesized chemicals with are generally designed for significant and targeted disruption of ongoing events.

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