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Minireview *Highlight Article*

Attenuation of acute and chronic inflammation using compounds derived from plants

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Impact statement

A large component of many disease states is the improper regulation of immune function. This commonly leads to the appearance of redundant inflammation which does not effectively address any underlying issue but actually impedes a successful response to disease-induced metabolic derangement. There is currently no means of successfully addressing this problem which is especially relevant in the ongoing viral pandemic of SARS-CoV-2. In view of this failure, new courses of action need to be contemplated. This review proposes reconsideration of the potential utility of natural compounds originating from plants in order to address this deficit. Such a new direction, in concert with more conventional strategies could help to alleviate this wide-ranging crisis.

Abstract

The appearance of excessive inflammatory activity is associated with onset of many disease states. Such non-productive responses are often the basis of the mortality consequent to incurring numerous disorders. The current outbreak of coronavirus disease 2019 caused by the virus "severe acute respiratory syndrome coronavirus 2" is a striking reflection of the inadequacy of current medical science to adequately address this issue. The usefulness of a range of materials of botanical origin in the attenuation of both chronic and acute inflammatory responses to various disease stressors is described. The properties of preparations of plant-based origin often parallel those of synthesized pharmacologics, but differ from them in some key respects. These differences can lead to more traditional preparations having distinct therapeutic advantages but also a number of specific shortcomings. The strengths and weaknesses of these materials are objectively contrasted with that of a more orthodox pharmacological approach. Each of these emphases in style has specific advantages and they should not be considered as competitors, but rather as accomplices in combating adverse states involving derangement of immune function.

Keywords: Inflammation, oxidative stress, inflammatory cytokines, SARS-CoV-2 virus, signaling pathways

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Introduction

The maintenance of homeostasis is a major property of organisms. This is especially pronounced in homeothermic species where the internal milieu is sustained in a constant manner despite external fluxes in temperature. In order to effect this, a range of potential metabolic strategies are available. The immune system is one such factor, designed to reverse changes resulting from pathogenic events especially bacterial or viral infection, and thus to restore equilibrium. A major component of the immune response is the inception of inflammatory events which can be most effective in containment and dispersal of contagious agents of exogenous origin. This system can also target and destroy intrinsically derived abnormal cells. However, the intrusion of a state of excessive and superfluous inflammation is pervasive in a remarkably large number of disease states, and is often for the most part untreatable.

Inappropriate inflammatory changes can take place precipitously in response to acute diseases. A rapid onset of high levels of inflammation can be lethal in a short time. The immediate cause of death of many infectious diseases is in fact due to such inflammatory activity. These changes result from cessation of relevant destruction of the pathogen, and transition to inappropriate activity which is no longer well-focused on the original invasive target species.

In the case of SARS-CoV-2 or influenza infection, cytokine responses emerge after viral infection of epithelial cells

followed by resident innate immune cells within the lung. This restrains further spread of the virus and activates other cell types that assist in elimination of the virus and enable the repair of lung tissue and ultimately inhibit inflammation. The acute inflammatory reaction is generally appropriately and rapidly resolved after an invading threat is successfully managed. However, it is common for a second wave of inflammatory responses to become extended for an undesirable period. This enduring state reflects failure of resolution of the inflammatory response. In these circumstances, failure to quench the intense immune hyperactive state can be life-threatening and accounts for most of the mortality of SARS-CoV-2.[1]

Undesirable inflammation can also take place at low levels for prolonged periods. Persistent low grade inflammation is thought to underlie most unresolved chronic disease states like diabetes, Alzheimer's disease, and cardiovascular diseases.[2,3] A chronic inflammatory state is also associated with normal aging and may contribute several of the hallmarks of senescence.[4]

The causal basis of both acute and chronic inflammation appears to be largely by way of identical pathways, involving the same transcription factors like IFN regulatory factor 5 (IRF5)[5] and NF-kB, and kinases such as Akt.[6]

To counteract undesirable inflammatory activity, a wide range of pharmacological strategies have been developed. Despite the development of many drugs, the goal of effective blocking of acute, often fatal inflammation has not been achieved. This is especially apparent with the recent pandemic of the SARS-CoV-2 virus. The regulation of the low level chronic inflammation associated with many age-related disorders has also not been successfully realized.

In view of this problem, it may be worthwhile to reconsider the potential of preparations of plant origin as a means of tackling this deficit. The goal of this article is to critically re-evaluate the utility of traditional herbal formulations. This review is confined to discussion of chemically defined and purified constituents of biological origin, rather than evaluation of unrefined and complex proprietorial blends such as those found in Chinese herbal medicines. There are many promising reports of anti-inflammatory activity of crude plant extracts, for instance those derived from *Sedum sarmentosum Bunge*.[7] Regrettably, despite identification of many flavonoids in this extract,[8] the critical bioactive components have not been distinguished. In view of the many variables involved, these mixtures containing a huge number of constituents cannot properly be scientifically appraised.

This review is not intended as a comprehensive survey. It is intended to highlight some key differences often found between natural and synthetic chemicals and to emphasize the potentially distinctive attributes of plant-derived chemicals that may be useful in contending with inflammatory diseases. Inflammation is prevalent in a persistent form in many age-related diseases, and in a more dramatically fulminating mode in the current viral SARS-CoV-2 pandemic. In view of its urgency, this contagion is emphasized in this review.

Contrasts between manmade pharmacological agents and those derived from traditional remedies

Advantages of modern synthetic chemical strategies in drug development

There are many advantages ensuing from use of well-defined chemicals as drugs. Use of herbal preparations containing poorly defined and complex mixtures of components can sometimes have unwanted consequences, due to the presence of toxic constituents. In such preparations, some ingredients have on occasion proved to be very harmful especially to the liver.[9,10]

The difficulty of reliably reproducing a complex formulation is also an adverse feature of traditional medicines. Materials derived from the same plant from different areas can have different compositions. The seasonal flux of plant metabolism is also another variable factor.

A very high degree of degree of focus is attempted in modern drug design, with a continual striving to achieve minimal undesirable side effects. Thus, there is an evolution toward ever greater potency and specificity leading to a progression of drugs with increasing effectiveness.

Advantages of traditional formulations

Herbal preparations can have varying degrees of homogeneity. Some may involve diverse chemicals from several different sources and are impossible to accurately describe. However, other products not considered as of true clinical value include single and well-defined species such as curcumin or glycyrrhizic acid. These types of chemical are likely to be less targeted toward a precise molecular site than are carefully designed modern drugs. However, the development of generalized inflammation is unlikely to be initiated at a single site of action and is likely to further develop through many pathways. The difficulty in treating it may be related to its multifactorial nature. Thus, a therapeutic agent lacking a very precise focus may have distinct advantages, possessing a penumbra of lesser but relevant properties. This may be useful, especially when contending with a broadly diffuse inflammatory state.

Despite the fact that some very potent biological toxins exist, older medicinal formulations which do not involve synthesis of novel compounds are less likely to represent a metabolic challenge following ingestion, than are molecular species which are wholly manufactured by novel synthetic processes. Chemicals of plant origin can also serve as a basis for later pharmacological chemical modification to provide drugs of improved specificity or potency.

The "cytokine storm" following SARS-CoV-2 infection consists of uncontrolled over-production of inflammatory agents including IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF-α).[11] The mechanisms of action of some synthetic and traditional medicines used to mitigate inflammation have many similarities and often act at the same loci.

The inhibition of these events whether by natural or synthetic agents, is key to enhancing survival rates.

Molecular targets of agents reducing inflammatory activity

Inhibition of NF-κB, TNF-α, iNOS, and inflammatory cytokines

Translocation of activated NF-κB to the nucleus is a key signaling pathway in the initiation of inflammatory activity following viral infection. Some of the major inflammatory proteins consequently synthesized are TNF-α, IL-1β, and IL-6 cytokines. Many manmade pharmacological means have been used to subdue this chain of events. These include direct blockade of TNF-α by etanercept,[12] fluoroquinolone antibiotics,[13] or use of recombinant monoclonal antibodies to TNF-α such as adalimumab.[14] Such antibodies specific for inflammatory cytokines such as TNF-α and IL-6 also show promise as potent means of diminishing the SARS-CoV-2-related cytokine storm.[15]

Many plant-derived materials have also shown promise in inhibiting the trajectory, whereby activation and nuclear translocation of NF-κB and other key transcription factors lead to derepression of DNA sites coding for cytokine mRNAs and thence to synthesis of inflammatory cytokines.[16] The neuroprotective effects of ginkgolide B and of a standardized extract of *Echinacea Purpurea* have been attributed to the inhibition of NF-κB.[17,18]

Chloroquine is a synthetic form of quinine, an antimalarial found in the bark of the Chinona tree. Both have multiple effects on the immune system cells including inhibition of the p38 MAPK pathway and of release of crucial pro-inflammatory cytokines.[19] The usefulness of chloroquine in the moderation of the SARS-CoV-2-initiated cytokine storm is also currently being evaluated but results have hitherto been equivocal.[20] Furthermore, this drug has significant systemic toxicity.[21] Fluoroquinolone antibiotics are man-made, but their development and molecular basis is derived from the quinine molecule. Compounds derived from by-products of chloroquine synthesis such as ciprofloxacin also possess a marked capacity for inhibition of NF-κB activation and thus lower production of inflammatory cytokines. They may therefore have significant potential moderation of the "cytokine storm".[13]

Inhibition of monocyte chemotactic protein 1

The "cytokine storm" following SARS-CoV-2 infection consists of uncontrolled over-production of inflammatory agents including IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF-α).[11] Similar events take place following infection with Middle East respiratory syndrome, MERS.[22] The inhibition of such events is key to enhancing survival rates.

Potent chemokine inhibitors with broad specificity have been evolved by viruses as a defense against host immune attack. These have been identified and purified and may have utility in subduing inflammatory events in a novel manner.[23] Extracts of aged *Allium sativum* have been found to reduce production of inflammatory cytokines and histamine. While such extracts are complex and of uncertain composition, the active constituents have been characterized and are well-defined. Aged garlic is rich in several organosulfur compounds, S-allyl-L-cysteine, S-allyl mercaptocysteine, allin and diallyl disulfide may also have evolved as anti-viral agents[24] and all possess anti-inflammatory properties.[25] Aged garlic extracts and S-allyl-L-cysteine have been shown to inhibit several pathological cascades that lead to synaptic degeneration and neuroinflammatory pathways.[26,27]

α1-adrenergic receptor antagonism

Catecholamines by acting on α1-adrenergic receptor sites can enhance inflammatory injury by activation of several transcription factors including NF-κB, thus enhancing production of inflammatory cytokines.[28] The resulting inflammation can be attenuated by blocking catecholamine synthesis or use of α1-adrenergic antagonists like prazosin or doxazosin.[29] These drugs have been shown to reduce mortality after induction of inflammation in experimental animals.[30] The α1-adrenergic receptor can also be blocked by the flavonoid galetin 3,6-dimethyl ether derived from the plant *Piptadenia stipulacea*.[31]

Stimulation of nicotinic cholinergic activity

3–(2,4-Dimethoxybenzylidene)-anabaseine, DMXBA, a derivative of the natural alkaloid anabaseine derived from nemertine worms, is a selective agonist of the nicotinic acetylcholine receptor, α7Ach. It has much less toxicity than nicotine but has an equally marked effect in suppressing the production of inflammatory cytokines.[32]

Inhibition of NLRP3 inflammasome activity

Activation of the Nod-like receptor protein 3 (NLRP3) inflammasome system is thought to be a major culprit in causing the chronic low level inflammation associated with a wide range of diseases, many of which have a strong relation to aging. These include Parkinson's disease, Alzheimer's disease, multiple sclerosis, depression, obesity, type 2 diabetes, cancer, and arthritis.[33] There are several metabolic sites at which the NLRP3 inflammasome can produce effects. The multiplicity of these sites and their likely blockade by specific phytochemicals has recently been documented.[32] Since a high level of NLRP3 inflammasome activation is associated with the development of the acute cytokine storm,[34] such a therapeutic potential takes on extra significance at the current time of SARS-CoV-2 prevalence. Ginkgolide B reduces NLRP3 inflammosome activation, by blocking the nuclear translocation of NF-κB.[35]

Release of extracellular HMGB1

HMGB1 (High mobility group box-1) can trigger pro-inflammatory cytokine release by the activation of TLR4 and other key receptors. It has been proposed as a therapeutic target for the treatment of SARS-CoV-2.[36] There are few modern man made drugs that act at this site but (–)-epigallocatechin-3-gallate (EGCG), derived from green tea can

block release of HMBG1 and protect mice from lethal endotoxemia.[37]

Blockade of the PAF receptor

Platelet-activating factor (PAF) is a phospholipid facilitator of inflammation that is released early in the inflammatory process by several cell types. Its effects depend on activation of the receptor PAF-R which has been associated with several immune-based disorders; allergies, asthma, and autoimmune diseases.[38]

Ginkgolide B, a terpene lactone derived from the *Ginkgo biloba* tree, antagonizes the PAF-R pathway, which leads to inhibition of activation of NF-κB. This can protect and alleviate the inflammatory response of alveolar epithelial cells from inflammatory damage and may thus be of use in reducing the severity of the virally induced cytokine storm.[39]

Oxidative stress

Dietary antioxidants like vitamins (vitamin C, vitamin E), and phytochemicals (carotenoids and polyphenols) in addition to preventing excess pro-oxidant activity, have anti-inflammatory properties. Dietary fiber, converted into short-chain fatty acids within the gut, also has anti-inflammatory properies.[40] The combination of ginseng with Vitamin C leads to activation T and NK immune cells while decreasing the intensity of lung virally induced lung infection.[41]

Quercin and quercetrin are well-defined flavonoids present in a wide range of plants. While they appear to act predominantly in an antioxidant manner, this can bring about distinct anti-inflammatory properties as well.[42] Quercetrin can mediate inhibition of macrophage polarization to the inflammatory M1 state, leading to decreased levels of iNOS and IL-12.[43] As inflammatory and pro-oxidant events are often closely linked, it can be difficult to unambiguously describe the precise site(s) of action of a phytochemical agent.

By acting as an anti-oxidant, epicatechin gallate, originating in green tea, can reduce inflammation and increase survival of influenza-infected mice.[44] Several other anti-oxidants including N-acetyl cysteine, glycyrrhizin, polyphenols, and ascorbate, may act in a parallel manner and could be protective against virally induced cytokine storm.[45]

The site of production of most reactive oxygen species within the cell is the mitochondrion. This organelle has also been proposed as a primary point of action of many protective phytochemicals.[46] However, the degree to which acting on the mitochondrion contributes to the overall effectiveness of these agents is not known.

Activation of endocannabinoid receptors

Cannabidiol (CBD) is a non-psychoactive component of *Cannabis sativa* with anti-inflammatory properties. While part of its activity is due to its binding to several distinctive CBD receptor species, it also acts at numerous other receptor systems and enzyme activities among which modulation of eicosanoid metabolism is a major factor.[47,48] As CBD is also able to downregulate the expression of the two key receptors for SARS-CoV-2 in isolated systems, it has been proposed as an ancillary drug in the treatment of SARS-CoV-2.[49] There is, however, a caveat concerning such use, namely the possibility that subduing the inflammatory response may leave an organism more vulnerable to infection. The use of CBD has been associated with elevated risk of incurring infectious disease.[50]

Phytochemicals with both anti-inflammatory and anti-cancer properties

Many phytochemicals that were originally reported to have anti-tumor properties have been subsequently found to be anti-inflammatory. These include the oligomeric epicatechin class of polyphenols[51] resveratrol, curcumin, quercetin, and isoflavone.[52] Such a dual capability is unsurprising since many of the key steps involved in carcinogenesis are related to inflammation. Curcumin has low solubility in water and is poorly absorbed by the gut, and concurrent application of piperidine as a vasodilator is used to remedy this. Overcoming this limitation may be critical in enhancing the value of curcumin in alleviating human disease.[53] Additionally, in order to circumvent this problem, several polymeric nanoparticle formulations of curcumin have been developed and their application has been shown to elevate curcumin levels in the brain and to create a more favorable redox and less inflammatory intracellular environment in several tissues.[54,55]

Sites of action of phytochemicals

Some of the drugs discussed here have well defined specific receptor targets. Melatonin probably acts predominantly by way of G protein-coupled MT_1 and MT_2, while cannabidiol largely but not exclusively acts at endocannabinoid CB1 and CB2 receptor sites. Rapamycin is a selective inhibitor of the mTOR (target of rapamycin) kinase.

The exact sites of primary action underlying the anti-inflammatory effects of many phytochemicals are generally less well known. Their targets are likely to involve binding at more than one site, leading to activation or inactivation of a specific sequence of metabolic events. There is evidence that curcumin impacts a wide range of targets[56,57] and this may be representative of the actions of most phytochemical drugs.

Owing to the low doses of phytochemicals that actually are found within cells, the mechanisms of action seem to primarily encompass targeting of components of classical inflammatory pathways leading to altered gene expression and production of mRNAs and miR. These transcriptional trajectories are capable of greatly magnifying the strength of the original triggering stimulus. Such amplifying sequences include receptor-initiated activation of a series of kinases (example; MAP kinases), thence leading to emergence of active transcription factors and their nuclear translocation. The genetic responses initiated by these signaling cascades then lead to the appearance of proteins like the NLRP3 inflammasome and inflammatory cytokines. This

extended series of sequential steps linking many components, can be subject to interference at a wide range of loci.

Some agents reported to act as antioxidants, are present in concentrations that are too low to allow them to act directly and effectively as free radical scavengers. For example, free melatonin is present at intracellular concentrations of 1.5–5 pM, and thus has a minute fraction of the direct antioxidant potency of glutathione, present in most cells at millimolar concentrations.[58] Many phytochemicals probably act by receptor activation leading to stimulation of a transcriptional sequence of events rather than directly as primary antioxidants. Despite the fact that they are only found within the cell in low concentrations, this allows them to act effectively by utilizing the magnifying properties of the intracellular signaling cascade.

In addition to its anti-mitotic properties, colchicine, derived from the Autumn crocus, has long been used as an anti-pyretic and anti-inflammatory. By inhibition of microtubule polymerization and interfering with intracellular transport, a variety of inflammatory pathways are inhibited in a distinctive manner.[59] Its potential utility in the treatment of SARS-CoV-2 is currently being examined.[60]

Stimulation of appropriate immune responses

Chronic immune activity throughout life is thought to lead to the accumulation of an enduring legacy of irresolvable damage. This can result in a persistent inflammatory state with aging which is further exacerbated in many diseases common in senescence.[61] Since the maintenance of effective immune defenses is essential throughout life, crude suppression of immune-related processes is inappropriate. Specific aspects of the immune response need to be targeted with meticulous precision. The moderation and appropriate redirection of immune reactivity is a critical process that should come after an intense inflammatory response. For example, the reactive M1 form of macrophages is vital to attack invading organisms, but this must later be converted to the more anabolic M2 form which is essential for the termination of inflammatory responses and commencement of anabolic activity.

There are several classes of drug possessing such immunomodulatory properties that may be candidates for, not merely in the blunt attenuation of inflammation, but in effecting the reconstruction subsequently needed.

Omega-3 fatty acids, ecosapentaenoic acid, docosapentaenoic acid (n-3DPA), and docosahexaenoic acid

These occur in fish oil and other seafood and can be metabolized to a class of chemicals; the resolvins.[62] The resolvins are active metabolites, synthesized during the initial phases of acute inflammation and can mediate its appropriate resolution. These events reflect enhancement rather than inhibition of normal immune functioning.[63] The dual combination of anti-inflammatory agents together with resolution mediators like resolvins and epoxyeicosatrienoic acids may block onset of the type of "cytokine storm" found with SARS-CoV-2 infection.[64]

Melatonin

Melatonin is a natural product of widespread occurrence in plants and animals which acts on immune function, both by inhibiting acute non-selective inflammation and by enhancing a desired immune response.[2] Melatonin can effect upregulation of SIRT-1 which leads to inhibition of pro-inflammatory NF-kB.[65] It has been proposed as a potential adjuvant in the treatment of SARS-CoV-2.[66] Melatonin does not act as an immune suppressant but redirects immune responses in a beneficial manner. Thus, when the reaction to an inflammatory stimulus is excessive in a young animals, this is attenuated by melatonin. Conversely, when such a reaction to an inflammogen is grossly diminished in an aged animal, melatonin will augment the immune response.[67] This exemplifies the subtle immunomodulatory capacity of melatonin.

Rapamycin

A natural product derived from the bacterium *Streptomyces hygroscopicus*, namely rapamycin (also known as sirolimus), was originally used as an immunosuppressant during organ transplantation. Rapamycin has now found broader use in protecting the virally infected lung from severe inflammatory damage,[68] suggesting its potential utility in the treatment of SARS-CoV-2. A significant attribute of rapamycin is its low renotoxicity.

The inhibition of mTOR (mammalian target of rapamycin) protein, a serine/threonine kinase that controls cell growth and metabolism is the major attribute of rapamycin. The mTOR network has an integrative function that can dictate and optimize inflammatory responses. Inhibition of mammalian target of rapamycin complex1 (mTORC1) in macrophages promotes autophagy, which is vital for pathogen killing but also enhances macrophage polarization to the non-inflammatory M2 form, concerned with anabolism.[69] The activity of mTORC1 activity is thus an important regulator of macrophage plasticity while being neither inherently pro-or anti-inflammatory.[70]

Ginkgolide B

Ginkgolide B can redirect microglia/macrophage polarization from the inflammatory M1 phenotype to the anti-inflammatory M2 form both *in vivo* and *in vitro*[71] and in this manner promote anabolic events.

Other compounds

Several phytochemicals with well-defined chemistry appear to attenuate inflammatory activity by several mechanisms acting in concert. These include resveratrol, curcumin, polyunsaturated fatty acids, and ginsenosides. A large range of molecular targets been described for each of these. Thus, curcumin appears to act on a range of transcription factors such as NF-kB, and kinases leading to altered expression of cytokines, and apoptosis-related proteins.[72,73] A significant outcome of these many branched sites of

action, is an increased ability to counter oxidative stress. Other mechanisms include suppression of production of inflammatory cytokines such as TNF-α together with enhancement of levels of anti-inflammatory interleukins.[74] Induction of miRNA species including miR-146a, promoting anti-inflammatory conditions can be induced by ginsenosides and proanthocyanidins, thus augmenting desirable immune responses while at the same time suppressing inflammation.[75] The regulation of miRNA expression may be a key site of action of phytochemicals.[76]

Conclusions

The substitution of plant-derived products for steroids and non-steroidal anti-inflammatory drugs in the regulation of inflammation can have marked advantages. Both steroids and NSAIDS are known to a have a substantial risk of serious side effects. Plant products such as curcumin, berberine, and epigallocatechin gallate that reduce inflammation tend to have a more diffuse spectrum of target sites than man-made pharmacologicals, and this may account for their lower toxicity.[77]

Furthermore, such an enhanced spectrum of molecular targets could result in an increased scope of the anti-inflammatory effects. For example, the combination of vitamin C, curcumin, and glycyrrhizic acid may have a synergistic potential against SARS-CoV-2 virus.[66] The events that may lead to a more than additive effect of various combinations of agents in furthering various anti-inflammatory signaling pathways have been discussed.[78]

The timing of the administration of anti-inflammatories during infection is important. An effective initial primary immune response to bacterial or viral invasion is essential to prevent dissemination of the disease. It is failure of resolution and repositioning of inflammation to lower levels, that requires rapid pharmacological intervention.

There are several reasons why phytochemicals have not been fully accepted by modern clinical pharmacology. A major feature is the prevalence of poorly defined blends of plant products which cannot be properly evaluated. Yet this should not reflect on the value of using an assembly of clearly defined and purified materials of plant origin. Another issue is the difficulty of the commercial development of drugs where obtaining exclusive rights are not possible and cannot lead to patenting of products. While this tends to make non-proprietorial phytochemicals relatively inexpensive, it may also discourage their promotion and distribution.

The utility of herbal preparations lies not in the use of ill-defined private blends but in the identification, purification, and testing of known chemicals and their subsequent pharmacological use. If needed, these can also then be formulated into multi component drugs in a reproducible manner. Such a perspective will remove the mystery of phytochemicals and allow their scientific development.

The best utilization of drugs is to be found when there is an effective alliance between appraising the validity of manmade and naturally derived agents. A collaborative rather than a competitive relationship is likely to further the best interests of patients.

The articles cited in this report were largely derived from databases of the National Library of Medicine search engine, together with some materials from Google Scholar.

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