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Can a plant-derived compound provide a lupus lifeline?

"If man can be convinced to follow a 'healthy diet' which includes tapping the beneficial effects of various plant sources, there is a ray of hope that this may lead to a healthier human species through epigenome engineering."

Keywords: inflammation • nutrition • plants • systemic lupus erythematosus • triterpenoids

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease in which a defective immune system is triggered to attack self-antigens through several dysregulated cell signaling pathways resulting in multiple target organ damage [1]. The ideal treatment for such a disease should support the immune system by normal regulation of various cytokines and immune mediators to bring back 'the homeostatic immune status' of the body. However, most of the current treatment options control disease by producing a generalized immunosuppressive state leading to a suboptimal or at times, even a worsening effect on the quality of life of patients, due to the side-effects of treatment. There have been extensive efforts in research, to elucidate the various mechanisms mediating autoimmune pathogenesis and to target specific effector pathways and receptors that are important for the autoimmune response, in an effort to optimize treatment for SLE.

Can a natural compound derived from plants provide an answer to our search for this ideal drug that inhibits the pathogenic signaling cascades to bring back the state of immune homeostasis? The idea is exciting, but how close this is to reality, can only be known from formal scientific research. All ancient medical systems rely mainly on plant-derived medicines and diet regulations as treatment options and for optimizing health. Was this solely due to easy availability or was this because it was a wise and effective method of treatment? Identifying such an effective natural compound or a template for synthetic modification may provide a treatment option for SLE, that is more cost–effective and with fewer side effects.

Many compounds derived from plants have been studied lately for its anti-inflammatory, antioxidant and immunomodulatory effects. Foremost among them are triterpenoids derived from the resins of trees which have been used in traditional Indian (Ayurvedic) system of medicine for treatment of various illnesses. Of these, a synthetic derivative of oleanoic acid, 2-cyano 2,3-dioxoolean-1,9-dien-28-oic acid (CDDO) was found to be 400-times more potent than others and had anti-inflammatory effects similar to dexamethasone, which is the main treatment modality in lupus [2]. Its derivative compounds CDDO-Me and CDDO-Im have potent anti-inflammatory and anticancer properties which are multifunctional [3]. CDDO-Me (bardoxolone methyl) is the C-28 methyl ester of CDDO and has been shown to block STAT-3 signaling [4,5], inhibit mitochondrial oxygen consumption and electron transport via perturbations in inner mitochondrial membrane fluidity [6], block the NF-κB pathway [7], inhibit the activation of ERK-1/2 and abrogate Bcl-2 phosphorylation [8]. Additionally, through the activation of the NF-E2-related factor (Nrf2)-dependent antioxidative pathway, CDDO-Me protects against lipopolysaccharide-mediated inflammatory responses [9]. In a Phase II clinical trial, CDDO-Me has been shown to improve the estimated glomerular filtration rate in patients with advanced chronic kidney disease and Type 2 diabetes mellitus [10].

In our own study to test the therapeutic potential of CDDO-Me in murine lupus

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nephritis, CDDO-Me was found to prevent or reverse the hematologic, autoimmune and pathological manifestations of lupus [11]. CDDO-Me-treated spontaneous lupus mouse models, B6 Sle1.Sle3 and MRL/lpr, exhibited significantly reduced splenic cellularity, with decreased numbers of CD4+ T cells and activated CD69+/CD4+ T cells compared with the placebo-treated mice. The two serum immune markers, anti-dsDNA and antiglomerular antibodies were significantly reduced. CDDO-Me treatment ameliorated renal disease in mice, as indicated by reduced proteinuria, blood urea nitrogen and glomerulonephritis. Dampening of MEK-1/2, ERK and STAT-3 signaling within lymphocytes occurred following CDDO-Me treatment. Of note, the Nrf 2 pathway was activated following CDDO-Me treatment, indicating that CDDO-Me may alleviate renal damage in lupus by inhibiting oxidative stress.

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Cyano enone of methyl boswellate extracted and modified from the ancient Indian medicinal plant *Boswelia Serrata* is another synthetic triterpenoid that has anti-inflammatory properties and structural similarity to CDDO [12]. Oleogum resins extracted from Boswellia have demonstrated anti-inflammatory properties with a mechanism different from that of NSAIDS, and related to components of the immune system. Clinical studies so far suggest efficacy in autoimmune conditions including rheumatoid arthritis, Crohn's disease, ulcerative colitis and bronchial asthma with comparatively minimal side effects [13]. There are no studies on the effectiveness of *Boswellia* extract in lupus, however its immunomodulatory effects in animal studies which includes suppression of immune hemolysis by inhibiting C3 convertase, enhancing phagocytic function of macrophages, inhibiting TNF-α through the NF-κB pathway and inhibition of TH1 cytokines without a generalized immune suppressive effect makes it a potential research molecule for therapeutic effectiveness in lupus [14–17]. Several additional triterpenoid derivatives are also known to have anti-inflammatory potential along with other therapeutic properties and have not so far been studied in autoimmune diseases, making the scope for future research in the field interesting and vast.

Targeting reactive oxygen species (ROS) mediated inflammatory glomerular damage in acute renal inflammation, using the green tea catechin, epigalocatechin-3-gallate (EGCG) was another natural treatment modality we investigated [18]. EGCG is a potent anti-inflammatory and antioxidant agent shown to inhibit leukocyte chemotaxis, quench free radicals, chelate transition metals and interrupt lipid peroxidation chain reaction. Our results showed amelioration of disease as evidenced by reduced proteinuria, normalization of serum creatinine and milder renal pathology with lesser macrophage and lymphocytic infiltrates compared with the vehicle treated controls. The renal oxidative stress markers malondialdehyde and hydrogen peroxide and the major source of ROS generation, NADPH oxidase were significantly elevated in vehicle treated anti-GBM mouse models compared with the EGCG treated diseased mice following treatment. NF-κB which is an important mediator of inflammation and immune response is activated by ROS and inflammatory cytokines. There was evidence of marked upregulation of activated p65/NF-κB in the vehicle treated mice compared with the EGCG treated diseased mice confirming the anti-inflammatory effect of EGCG.

Our very recent study demonstrated therapeutic effectiveness of polyphenolic compound 'curcumin' in the treatment of acute and chronic forms of immune nephritis in lupus and elucidated the mechanism of its action on various signaling pathways in B cells which are known to be involved in pathogenesis of lupus. Curcumin is isolated from the rhizome of medicinal plant *Curcuma longa* and it is the yellow pigment in the Indian spice 'turmeric'. Renal disease, assessed by proteinuria, serum creatinine, serum autoantibody levels and renal histology showed significant improvement supporting the existing data from a randomized placebo controlled trial on the effectiveness of curcumin treatment in reducing proteinuria, hematuria and blood pressure in patients with refractory or relapsing lupus nephritis [19]. The blood counts and liver function tests post treatment in the acute and chronic nephritis mouse models showed no significant difference in both treatment groups, ruling out major side effects with treatment.

In addition to expansion of research to identify novel therapeutic agents belonging to the plant kingdom, an important aspect for further progress is intensifying research on each of these identified compounds, to understand pharmacokinetic properties, establish the effective dose and to rule out side effects or toxicity, in a systematic fashion. Even though they are plant derived or might have been used as traditional medicine or food additives since ancient days, many of these compounds

studied are modified synthetic derivatives or used at a high dose, mostly in patients with other comorbidities or disease manifestations pertaining to multiple organ systems. CDDO-Me or bardoxolone methyl was evaluated by a Phase III clinical trial in patients with Type 2 diabetes mellitus and stage 4 chronic kidney disease. The trial used a longer duration of drug exposure and amorphous spray dried formulation of drug at a fixed dose in patients with more severe chronic kidney disease (CKD) compared with previous trials (which showed effectiveness in reducing renal disease through Nrf2 pathway activation) and had to be terminated due to increased heart failure events, of which many were due to fluid overload [20]. On further analysis of the study data it is interpreted that, the adverse effect which was not seen in healthy subjects and early stages of CKD with bardoxolone treatment is possibly due to fluid retention by regulatory effects of CDDO-Me on the endothelin pathway, which is exaggerated in the presence of excess endogenous endothelin-1, as seen in advanced CKD patients [21]. Therefore the effective dose, mode and form of drug administration and the possible interactions with functioning of compromised organ systems should be carefully considered even while using plant-derived compounds.

The challenge that arose in clinical trials using curcumin is the extremely poor bio-availability achieved in Phase II clinical trials in cancer patients [22]. Combining curcumin with black pepper extract piperine, has shown to considerably increase bioavailability in animals and human volunteers [23]. The traditional Indian cuisine combines turmeric with black pepper, while other studies mention turmeric in its whole form with the full spectrum of curcuminoids to be superior to curcumin. Does this also imply that including these plant-products in their natural form in diet can have a preventive effect on various inflammatory and oxidative damage mediated illnesses?

These are challenging questions for the future. Perhaps a bi-pronged approach ought to be adopted. On the one hand, scientists should intensify their efforts to identify (and biochemically optimize) active ingredients from implicated plant-derived candidates, and determine the optimal dosing and delivery regimes. On the other hand, efforts should be instituted to gradually modify societal dietary habits based on solid evidenced-based science. Along these lines, one is encouraged to note that dietary patterns can indeed modify gene expression, based on a recent study [24]. If man can be convinced to follow a 'healthy diet' which includes tapping the beneficial effects of various plant sources, there is a ray of hope that this may lead to a healthier human species through epigenome engineering.

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