

Putative Prophylaxes of Aloe vera Latex and Inner Gel as Immunomodulator

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Received: January 2, 2015

Revised: February 9, 2015

Accepted: February 12, 2015

Published online: May 21, 2015

ABSTRACT

Some of the phytochemicals present in *Aloe vera* can provide relief to rheumatoid arthritis (RA) patients through promoting wound healing as well as reducing inflammation and relieving pain, which are common symptoms of RA patients. Emodin in *Aloe vera* latex inhibited various inflammation kinases and signaling pathways in vitro and in vivo models of pancreatitis, arthritis and atherosclerosis. Novel molecular targets of emodin have been revealed in therapeutic uses based on animal studies, but only limited data related to the bioavailability, pharmacokinetics and metabolism of emodin are available till now. Western blot and quantitative PCR confirmed aloe emodin in *Aloe vera* latex up-regulating galectin-3 expression; recombinant galectin-3 augmented expression of antiviral genes IFN- β /r, PKR and 2',5'-oligoadenylate synthase in infected cells, agreeing with expression pattern of those treated with aloe emodin. Galectin-3 which is a β -galactoside-binding animal protein, is evolutionarily highly conserved and it has been demonstrated in RA patients to advance the transformation of synovial fluid into fibrotic tissue, in addition to activating osteoclasts, producing severe debilitation in patients. More work of emodin and aloe emodin needs to be done to fully translate the observed preclinical findings in RA and related complications. Aloe pectins obtained from *Aloe vera* inner leaf gel were distinguished by size: the room temperature extraction generated a high molecular weight (HMW), whereas extraction with heating produced a low molecular weight pectin. The HMW aloe pectin calcium gel is highly efficient encapsulating agent suitable for controlled release of

pharmacological substance, such as protein, antibodies and vaccines. Inhibition of galectin-3 mediated cellular interaction by pectin from dietary sources, such as citrus pectin, was revealed through haemagglutination significantly. The up-regulation of galectin-3 expression by potential therapeutics, such as emodin, aloe emodin, aloe pectin was focused in present review. In addition, protein and/or lectin having anti-inflammatory, radical scavenging and anti-oxidant enzymes' activity in *Aloe vera* gel were fully expected as putative prophylactic and biological response modifiers in the treatment of a broad range of inflammatory diseases such as RA.

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Key words: Putative prophylaxes; *Aloe vera* latex and inner gel; Aloe pectin/protein/lectin; Immunomodulator

Yagi A. Putative Prophylaxes of *Aloe vera* Latex and Inner Gel as Immunomodulator. *Journal of Gastroenterology and Hepatology Research* 2015; 4(5): 1585-1598 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1205>

INTRODUCTION

The aloe plant part is identified term and definition according to international aloe science council (IASC) as follow: (a). Plant part-leaf: The green rind or cuticle of the *Aloe vera* plant. The part of the *Aloe vera* plant utilized in commerce where processing is begun without stripping off of the rind; (b). Plant part-inner gel leaf: The *Aloe vera* inner leaf stores the *Aloe vera* gel; (c). Gel: Liquid product typically derived from the inner leaf that may contain pulp, and may or may not have added thickening agents (which must be identified on the label). (d). Plant part-aloe latex: The *Aloe vera* outer leaf pulp contains latex and anthraquinones. Brown, yellow-brown, or occasionally red exudated found in between the rind and inner leaf. Also called "sap", it contains several constituents, but most notably anthraquinone; (e). Whole leaf: This terminology is seen on product or in reference to raw material where the entire leaf is used as a

starting ingredient to create *Aloe vera* juice. The IASC recognizes this terminology to be accurate only if no purification, filtration or other treatment (enzyme, etc) is conducted on the ingredient beyond removal of any insoluble material; (f). Activated charcoal filtrated: A form of filtration using activated charcoal; utilized primarily to remove anthraquinones; (g). De-colored: A process, usually by filtration with activated charcoal. That makes the liquid aloe mass clear.

There are two types of processed *Aloe vera* juice that are used in commercially available products today: *Aloe vera* leaf juice and *Aloe vera* inner leaf juice. *Aloe vera* leaf juice is obtained grinding or macerating the entire *Aloe vera* leaf, then removing the rind material and the bitter, yellow substance (called "aloe latex"), typically through filtration via activated charcoal. *Aloe vera* inner leaf juice (some products can also be seen labeled as "gel", "inner leaf fillet" and "fillet gel") is manufactured by stripping off the outer rind of the leaves by machine or by hand, rinsing or washing away the aloe latex, then collecting and transferring the remaining inner leaf material, a gelatinous substance, for further processing into juice. Both of the aforementioned *Aloe vera* juice processes remove virtually all of the aloe latex substance, which is naturally occurring in the botanical and can be found in between the rind and the inner leaf material. Aloe latex contains a constituent called aloin (α and β); α - or β -linked C-glycoside anthrone, which is known to have strong laxative properties, aloe emodin and emodin. IASC has established a quality standard of <10 mg of aloin per liter of *Aloe vera* juice products for oral consumption^[1].

The present review shows prophylaxes of aloe latex; mainly emodin and aloe emodin, and aloe inner gel; pectin/protein/lectin, and *Aloe vera*, to rheumatoid arthritis, and immunomodulatory efficacy.

ALOE VERA-TISSUE MICROSCOPIC ANATOMY AND ALOE LATEX

The inner parenchymal tissues are divided into two zones, an outer layer composed of vascular bundles, which consist of a series of tubules which run the long dimension of the leaf just beneath the green epidermis; between the vascular bundles but on the same plane are found the large mesophyll cells called the outer lacunae or lacunar mesophyll. The second layer of the parenchyma, located deeper to the vascular bundles and the lacunar mesophyll cells, is comprised of small spongy mesophyll cells, which serve the function of water storage and help maintain the plant when exposed to hot, arid climates. The spongy mesophyll contains 99.5% water and a wide array of other substances, but is essentially devoid of anthraquinones. Throughout the spongy mesophyll is a series of small "veins" or plant vascular channels whereby water may be moved from the xylem tubules of vascular bundles into the spongy mesophyll for storage. These veins provide a network or grid of semisolid fibers, composed chiefly of polysaccharides, which give the spongy mesophyll its characteristic gel-like consistency. These vessels comprise the "pulp" of *Aloe vera*. It becomes obvious that the spongy mesophyll material may become contaminated with the yellow sap or anthraquinone-containing lacunar cell sap if the vascular bundle/lacunar mesophyll layer is not completely removed in preparation of the internal fillet gel or inner leaf fillet. The same contamination can occur with handfilling procedures if the fillets are not well rinsed of yellow sap and clear anthraquinone-containing fluid from the outer lacunar cells. Thus, commercial products provide a range of colors depending upon the manner of processing of the leaves. Also the amount of

aloe latex varies significantly with the season of the year becoming maximal in the fall months after long hot summer. Wide variations in anthraquinone levels in aloe latex may be seen from batch to batch.

TOXICITY OF EMODIN

Aloe vera is best known for two distinct preparations: the clear mucilaginous gel that is widely used for the treatment of minor burns, especially sunburns, and the thick sap of the leaves that turns yellow-brown and has strong laxative effects. *Aloe vera* is rich in vitamins, minerals, enzymes, sugars, anthraquinones (aloe emodin, aloin, and emodin) and salicylic acid, etc, however, most of its health benefits have been attributed to the polysaccharides found in the gel of leaves. The authors compiled some properties of *Aloe vera* with its medicinal uses^[2].

National toxicology program: Toxicology and carcinogenesis studies of emodin feed studies in F344/N rats and B6C3F1 mice was demonstrated. In conclusion, there was no evidence of carcinogenic activity of emodin in male F344/N rats exposed to 280, 830 or 2,500 ppm under the conditions of 2-year feed studies. There was equivocal evidence of carcinogenic activity of emodin in female F344/N rats based on a marginal increase in the incidence of Zymbal's gland carcinoma. There was equivocal evidence of carcinogenic activity of emodin in male B6C3F1 mice based on a low incidence of uncommon renal tubule neoplasms. There was no evidence of carcinogenic activity of emodin in female B6C3F1 mice exposed to 312, 625, or 1,250 ppm. Exposure of rats to emodin resulted in increased incidences of renal tubule hyaline droplets and pigmentation in males, increased incidences of renal tubule hyaline droplets in females, and increased severities of renal tubule pigmentation in males and females. Emodin exposure resulted in increased incidences of renal tubule pigmentation in male and female mice and increased incidences of nephropathy in female mice. Incidences of mononuclear cell leukemia decreased in male and female rats exposed to 2,500 ppm^[3].

EMODIN AS AN IMMUNOMODULATORY AGENT

The polysaccharide and flavonoid concentrations of two-, three-, and four-year-old *Aloe vera* were determined, and their antioxidant activities were evaluated compared to BHT and α -tocopherol by the DPPH radical scavenging method and the linoleic acid system at 100 μ g of soluble solids per mL of ethanol. The growth stage plays a vital role in the composition and antioxidant activity of *Aloe vera*^[4]. There is no doubt that antioxidants are necessary components for our health but we do not forget that the antioxidants and free radicals production should be in balance. Some free radicals are good in that they enable our body to fight inflammation, kill bacteria, and control the tone of smooth muscles, which regulate the working of internal organs and blood vessels. On the other hand increased or uncontrolled free radical activity might combine with other factors to cause some diseases such as neuro-degenerative diseases, heart disease, cancers etc. Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells. The pathogenesis of this disease is linked predominantly with the formation of free radicals at the site of inflammation.

The authors reviewed the data on diseases which may be linked to free radicals in order to clarify the role of free radicals in ethiopathogenesis of diseases^[5].

The authors investigated the possible mechanism of immunosuppressive effect of emodin. Human mononuclear cells (10^6 cells/mL) were stimulated with 0.25% phytohemagglutinin for 24, 48 and 72 h, and the proliferative response was determined by the uptake of 3H-thymidine. In the presence of emodin (10^{-6} to 3×10^{-5} M), the proliferative response was reduced in a dose-dependent manner. Emodin (3×10^{-7} to 3×10^{-5} M) also dose-dependently reduced the proliferative response to mixed lymphocyte reaction. After 72 h exposure to emodin (10 μ M), interleukin-1 (IL-1), IL-2 production and IL-2 receptor expression were all reduced. The structure-activity relationship of emodin and 10 other anthraquinone derivatives indicates that the free hydroxyl group at the β -position of the anthraquinone nucleus plays an important role in the immunosuppressive effect. The suppressive activity of emodin was significantly inhibited by catalase (a scavenger of hydrogen peroxide), but little affected by superoxide dismutase (a scavenger of superoxide radical) and mannitol (a scavenger of hydroxyl radical). Methylene blue and hemoglobin, guanylate cyclase inhibitors, did not significantly affect the suppressive activity of emodin. Nordihydroguaiaretic acid (a lipoxygenase inhibitor) significantly potentiated the suppressive activity whereas quinacrine (a phospholipase A2 inhibitor) and indomethacin (a cyclooxygenase inhibitor) did not significantly affect it. The results suggest that the immunosuppressive effect of emodin may be partly mediated through hydrogen peroxide generated from semiquinone and regulated by arachidonic acid metabolites or byproducts^[6].

The authors established the rats model of chronic fibrosing pancreatitis and proved the anti-fibrotic effect of emodin in chronic pancreatitis with fibrosis. **Methods:** Fifty rats were randomly divided into five groups, 10 rats in each group. Trinitrobenzene sulfonic acid (TNBS) was infused into the pancreatic duct to induce chronic pancreatitis in rats (except for normal group). Emodin-treated rats were fed with different doses of emodin (20, 40 and 80 mg/kg body weight) for 28 d, while normal group and control group received 0.9% sodium chloride solution. Serum levels of hyaluronic acid (HA) and laminin (LM) were determined by radioimmunoassay. Histopathological alterations were studied by optical microscopy. Expression of collagen was also examined while transforming growth factor- β -1 (TGF- β -1) was localized by immunohistochemistry. **Results:** In emodin-treated rats, the serum levels of HA and LM were decreased significantly (HA, 62.2 ± 19.3 μ g/L, $p < 0.05$); the degree of fibrosis was ameliorated observably; the expression of collagen in pancreatic tissue was reduced especially in high-dose emodin-treated group ($36\% \pm 5\%$ vs $42\% \pm 6\%$, $p < 0.05$); with the increased doses of emodin, the expression of TGF- β -1 was declined, compared with those in control group. **Conclusion:** Emodin has an anti-fibrotic effect on pancreatic fibrosis in rats. Because of its anti-fibrotic effect, it could be a potential herbal drug for the treatment of chronic pancreatitis^[7].

The authors investigated the immunosuppressive effects of emodin and its potential *in vivo* and *in vitro* mechanisms. **Methods:** *In vitro* immunosuppressive effects of emodin were analyzed by its ability to suppress the response of human peripheral blood mononuclear cells to phytohemagglutinin (PHA) and to mixed lymphocyte culture (MLC). The authors examined changes in IL-2 and -4 in which MLC supernates. The *in vivo* immunosuppressive effects of emodin were analyzed using a skin transplantation model in mice. The authors also investigated the mean survival time (MST) and plasma IL-2 levels. **Results:** *In vitro* experiments: Responses of mononuclear cells to PHA and MLC were suppressed by emodin treatment. Decreased production of IL-2 along with promoted secretion of IL-4 was also observed by emodin treatment during MLC. *In vivo* experiments:

The emodin-treated group showed prolonged MST of skin grafts and decreased serum IL-2 production. **Conclusions:** Emodin showed immunosuppressive activities both *in vitro* and *in vivo*. The potential immunosuppressive mechanism of emodin may be suppression of lymphocyte proliferation and influences on cytokines^[8].

Chronic inflammation of rheumatoid arthritis (RA) is promoted by proinflammatory cytokines and closely linked to angiogenesis. The authors investigated the anti-inflammatory effects of emodin in IL-1 β and lipopolysaccharide (LPS)-stimulated RA synoviocytes under hypoxia. Emodin significantly inhibited IL-1 β and LPS-stimulated proliferation of RA synoviocytes in a dose-dependent manner under hypoxic condition. Also, enzyme linked immunosorbent assay (ELISA) revealed that emodin significantly reduced the production of pro-inflammatory cytokines [tumor necrosis factor- α (TNF- α), IL-6/-8], mediators [prostaglandin E2, matrix metalloproteinase (MMP)-1 and -13] and vascular endothelial growth factor (VEGF) as an angiogenesis biomarker in IL-1 β and LPS-treated synoviocytes under hypoxia. Consistently, emodin attenuated the expression of cyclooxygenase 2, VEGF, hypoxia inducible factor 1, MMP-1 and -13 at mRNA level in IL-1 β and LPS-treated synoviocytes under hypoxia. Furthermore, emodin reduced histone deacetylase (HDAC) activity as well as suppressed the expression of HDAC1, but not HDAC2 in IL-1 β and LPS-treated synoviocytes under hypoxia. Overall, these findings suggest that emodin inhibits proinflammatory cytokines and VEGF productions, and HDAC1 activity in hypoxic RA synoviocytes^[9].

The authors evaluated the role of matrix metalloproteinase 1 (MMP-1), MMP-3, and tissue inhibitor of MMP-1 (TIMP-1) in the pathogenesis of joint inflammation and articular erosions in early inflammatory arthritis. **Methods:** Untreated patients with joint symptoms for <2 years were evaluated at presentation and followed up prospectively for 18 months. Swollen joint count and serum levels of C-reactive protein (CRP) were determined every 6 months. Serum levels of MMP-1, MMP-3, and TIMP-1 were measured by double-antibody sandwich enzyme-linked immunosorbent assay at the same time intervals. The number of joint erosions in serial radiographs of the hands and feet was also recorded. Analysis of synovial fluid levels of MMPs and TIMP-1 at presentation was completed in some patients. **Results:** Of 175 patients evaluated baseline, 85 had rheumatoid arthritis (RA), 39 had seronegative spondylarthropathy, 38 had undifferentiated arthritis, and 13 had self-limiting arthritis. Of 164 patients with available radiographs of the hands and feet at presentation, 33 (20.1%) had joint erosions. Baseline levels of MMP-1, MMP-3, and TIMP-1 were significantly higher ($p = 0.0001$, $p = 0.013$, and $p = 0.0001$, respectively) and ratios of TIMP-1: MMP-1 and TIMP-1: MMP-3 were significantly lower ($p = 0.0001$ and $p = 0.013$, respectively) in RA versus non-RA patients. In RA patients, serum levels of CRP correlated with MMP-3 and TIMP-1 levels, but not with MMP-1 and MMP-3, but not with levels of TIMP-1. One hundred one patients were followed up for the next 18 months. The number of patients with erosions and the number of erosions per patient increased significantly during this period. Area under the curve (AUC) measurements of MMP-1 and TIMP-1 levels, but not of MMP-3 levels, yielded significantly higher values in RA than in non-RA patients. In RA patients, only the AUC level of MMP-3 correlated with the AUC CRP level ($r = 0.67$, $p = 0.0001$), while only the AUC level of MMP-1 correlated with the number of new joint erosions ($r = 0.28$, $p = 0.034$). **Conclusion:** These data suggest an uncoupling of the pathophysiologic mechanisms associated with joint inflammation and articular erosion. Treatments that inhibit the production and activity of MMP-1 may preferentially limit the formation of new

joint erosions and improve the long-term functional outcome of some patients with inflammatory arthritis^[10].

Matrix metalloproteinase-3 (MMP-3) is involved in the immunopathogenesis of rheumatoid arthritis (RA), but little is known about its relationship to genetic susceptibility and biomarkers of disease activity, especially acute phase reactants in early RA. MMP-3 was measured by ELISA in serum samples of 128 disease-modifying, drug-naïve patients and analysed in relation to shared epitope genotype, a range of circulating chemokines/cytokines, acute phase reactants, autoantibodies, cartilage oligomeric protein (COMP), and the simplified disease activity index (SDAI). MMP-3 was elevated >1.86 ng/mL in 56.25% of patients ($p < 0.0001$), correlated with several biomarkers, notably IL-8, IL-6, INF- γ , VEGF and COMP (r values=0.22-0.33, $p < 0.014$ -0.0001) and with C-reactive protein (CRP) and serum amyloid-A protein (SAA) levels ($r = 0.40$ and 0.41 , resp., $p < 0.0001$) and SDAI ($r = 0.29$, $p < 0.0001$), but not with erosions or nodulosis. However, the correlations of CRP and SAA with SDAI were stronger (respective values of 0.63 and 0.54, $p < 0.001$ for both). COMP correlated with smoking, rheumatoid factor, and MMP-3. MMP-3 is significantly associated with disease activity, inflammatory mediators and cartilage breakdown, making it a potential biomarker of disease severity, but seemingly less useful than CRP and SAA as a biomarker of disease activity in early RA^[11].

The authors aimed to clarify the usefulness of bone, cartilage, and synovial biomarker in the management of rheumatoid arthritis (RA) therapy in remission. Synovial biomarkers: High matrix metalloproteinase-3 (MMP-3) levels are associated with joint progression in RA patients, but there is no data about their utility in clinical remission. Nitratid type III collagen and Glc-Gal-pyridinoline seem to be more specific to synovium, but more studies are required. Cartilage biomarkers: Unbalance between cartilage break-down biomarkers (Urinary CTX II and COMP) and cartilage biomarker (PIIANP) was described. This unbalance is also associated with joint destruction and prognosis of destruction. No data are available on patients in remission. Bone biomarkers: RA activity is correlated with an increase of bone resorption markers such as collagen type II C-telopeptide, CTX I, PYD, and TRACP 5b (a catabolic bone marker) and a decrease of bone formation markers such as osteocalcin and the alkaline phosphatase bone isoenzyme. RA therapies seem to improve bone turnover in limiting bone resorption. There is no study about bone marker utility in remission. **Conclusion:** Biomarkers seem to be correlated with RA activity and progression. They also could be used to manage RA therapies. The only biomarker with enough promising results is MMP-3^[12].

The authors investigated whether emodin treatment would modulate the severity of the disease in an experimental collagen-induced arthritis. **Methods:** The authors evaluated the effects of emodin on collagen-induced arthritis (CIA) mice. **Results:** The pathological processes of rheumatoid arthritis (RA) are mediated by a number of cytokines and MMPs. Expression of these proinflammatory mediators is controlled by nuclear factor- κ B (NF- κ B). This study was performed to explore the effect of emodin on control of the NF- κ B activation pathway and to investigate whether emodin has anti-inflammatory effects in CIA mice *in vivo*. Emodin inhibited the nuclear translocation and DNA binding of NF- κ B subunits, which were correlated with its inhibitory effect on cytoplasmic I κ B α degradation in CIA mice. These events further suppressed chemokine production and MMP expression. In addition, emodin inhibited the osteoclast differentiation induced by macrophage colony stimulating factor and receptor activation of NF- κ B ligand in bone marrow macrophages. **Conclusion:** These findings

suggest that emodin exerts anti-inflammatory effects in CIA mice through inhibition of the NF- κ B pathway and therefore may have therapeutic value for the treatment of RA^[13].

Recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is currently under clinical trials for cancer, however many tumor cells, including hepatocellular carcinoma (HCC) develop resistance to TRAIL-induced apoptosis. Hence, novel agents that can alleviate TRAIL-induced resistance are urgently needed. The authors investigated the potential of emodin to enhance apoptosis induced by TRAIL in HCC cells. As observed by MTT cytotoxicity assay and the externalization of the membrane phospholipid phosphatidylserine, the authors found that emodin can significantly potentiate TRAIL-induced apoptosis in HCC cells. When investigated for the mechanism(s), the authors observed that emodin can downregulate the expression of various cell survival proteins, and induce the cell surface expression of both TRAIL receptors, death receptors (DR) 4 as well as 5. In addition, emodin increased the expression of C/EBP homologous protein (CHOP) in a time-dependent manner. Knockdown of CHOP by siRNA decreased the induction of emodin-induced DR5 expression and apoptosis. Emodin-induced induction of DR5 was mediated through the generation of reactive oxygen species, as N-acetylcysteine blocked the induction of DR5 and the induction of apoptosis. Also, the knockdown of X-linked inhibitor of apoptosis protein by siRNA significantly reduced the sensitization effect of emodin on TRAIL-induced apoptosis. Overall, the experimental results clearly indicate that emodin can indeed potentiate TRAIL-induced apoptosis through the downregulation of antiapoptotic protein, increased expression of apoptotic proteins, and ROS mediated upregulation of DR in HCC cells^[14].

AMP-activated protein kinase has been described as a key signaling protein that can regulate energy homeostasis. The authors demonstrated that emodin enhanced GLUT4 translocation and ¹⁴C glucose uptake into the myotube in an AMP-activated kinase (AMPK)-dependent manner and inhibited glucose production by suppressing the expression of key gluconeogenic genes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, in hepatocytes. Furthermore, the authors found that emodin can activate AMPK by inhibiting mitochondrial respiratory complex I activity, leading to increased reactive oxygen species and Ca²⁺/calmodulin-dependent protein kinase activity. Finally the authors confirmed that a single dose administration of emodin significantly decreased the fasting plasma glucose levels and improved glucose tolerance in C57Bl/6J mice. Increased insulin sensitivity was also confirmed after daily injection of emodin for 8 days using an insulin tolerance test and insulin-stimulated PI3K phosphorylation in wild type and high fat diet-induced diabetic mouse models. The present study suggests that emodin regulates glucose homeostasis *in vivo* by AMPK activation and that this may represent a novel therapeutic principle in the treatment of type 2 diabetic models^[15]. In an earlier pre-clinical study, the treatment of aloe high molecular weight fractions of acemannan and aloe pectin in gel for hepatic fibrosis and type 2 diabetes was demonstrated, suggesting a possible contribution of barbaloin contaminated less than 10 ppm^[16].

The anti-inflammatory effects of emodin have been exhibited in various *in vitro* and *in vivo* models of inflammation including pancreatitis, arthritis, asthma, atherosclerosis and glomerulonephritis. As an anti-cancer agent, emodin has been shown to suppress the growth of various tumor cell lines including hepatocellular carcinoma, pancreatic, breast, colorectal, leukemia, and lung cancers. Emodin is a pleiotropic molecule capable of interacting with several major molecular targets including NF- κ B, casein kinase II, HER2/

neu, HIF-1 α , AKT/mTOR, STAT3, CXCR4, topoisomerase II, p53, p21, and androgen receptors which are involved in inflammation and cancer. The authors summarized reported anti-inflammatory and anti-cancer effects of emodin, and re-emphasized its potential therapeutic role in the treatment of inflammatory diseases and cancer^[17].

Emodin has been reported to regulate energy metabolism. Differentiated C2C12 myotube and 3T3-L1 adipocytes were treated with or without emodin of different concentrations for indicated time. Then glucose metabolism, oxygen consumption, lactic acid levels, glucose levels and inflammation pathways were detected. Cells were collected for quantitative PCR and western blot analysis. Emodin induced up-regulation of glucose uptake and consumption in both C2C12 myotubes and 3T3-L1 adipocytes, with glycolysis increased. Furthermore, emodin inhibited lipolysis under basic condition and in presence of TNF- α in 3T3-L1 adipocytes, while a significant decrease of p-perilipin was detected after emodin treatment. Moreover, emodin inhibited NF- κ B and ERK pathways in C2C12 myotubes and 3T3-L1 adipocytes. In conclusion, emodin up-regulates glucose metabolism, decreases lipolysis and inhibits inflammation in C2C12 myotubes and 3T3-L1 adipocytes^[18].

The effect of emodin on diabetic cardiomyopathy (DCM) was investigated in a type 2 diabetes mellitus (DM) induced in rats by low dose streptozotocine combined with high energy intake. Emodin-treated groups displayed significantly higher body weight (BW) and lower heart weight (HW)/BW. Furthermore, emodin could significantly decrease blood glucose, total cholesterol levels, and triglyceride levels in diabetic rats. Moreover, the emodin-treated group showed a marked increase in heart rate and showed lower left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular posterior wall thickness, and inter-ventricular septal diastolic wall thickness. Emodin induced a significant increase in phosphorylation of Akt and GSK-3 β in myocardium. These results suggest that emodin may have great therapeutic potential in the treatment of DCM by Akt/GSK-3 β signaling pathway^[19].

It has been suggested that the formation of osteoblasts in bone marrow is closely associated with adipogenesis, and the balance between osteogenesis and adipogenesis differentiation of mesenchymal stem cells (MSCs) is disrupted in osteoporosis. In order to improve the treatment of osteoporosis, available agents with roles of regulating the balance is highly desirable. Emodin has been used to treat bone diseases for thousands of year. However, the underlying molecular mechanisms of emodin in modulating osteogenesis and adipogenesis remain poorly understood. **Methods:** The molecular mechanisms of emodin on the processes of osteogenesis and adipogenesis in ovariectomized mouse and bone marrow mesenchymal stem cells (BMSCs) have been studied. Female ICR mice were assigned to three groups: sham group, ovariectomy group, emodin group. Efficacy was evaluated by H&E, immunohistochemical assay and Micro-CT. *In vitro*, the authors analyzed the effect of emodin-at concentrations between 0.1 μ M and 10 μ M-on the processes of inducing osteogenesis and inhibiting adipogenesis in BMSCs by ALP, Oil red O staining, real time RT-PCR and western blot. **Results:** It was shown that emodin could increase the number of osteoblast, bone mineral density, trabecular bone volume fraction, trabecular number and connectivity density of ovariectomized mice and decreased the bone marrow fat tissue and adipocytes. The genes and proteins expression of osteogenesis markers, such as Runx2, osterix, collagen type I, osteocalcin, or ALP were up-regulated. While, the genes and proteins involved in adipogenesis, PPAR gamma, C/EBP α and ap2 were down-

regulated. **Conclusion:** It was proved that emodin inhibits adipocyte differentiation and enhances osteoblast differentiation from BMSCs^[20].

Emodin has been reported to have anti-inflammatory, antibacterial, and antitumor activities. However, the effect of emodin on collagen-induced arthritis (CIA) has not yet been investigated. The authors investigated whether emodin has a protective effect against collagen-induced arthritis in mice and its possible mechanisms. **Methods:** CIA was induced in mice by immunization with bovine type II collagen. The mice were treated with emodin (5, 10, and 20 mg/kg/day, i.g.) from days 21 to 42 after immunization. The clinical scores and hind paw swelling were evaluated, The expression of prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) in synovial tissues was determined. The levels of tumor necrosis factor α (TNF- α) and interleukin-6 (IL-6) in the plasma were measured by enzyme-linked immunosorbent assay. **Results:** Emodin treatment significantly alleviated the severity of the disease, based on the reduced hind paw swelling and clinical scores, comparing with untreated CIA mice. Comparing with untreated CIA mice, emodin treatment inhibited the levels of TNF- α and IL-6 in the plasma, PGE2 production, and COX-2 protein expression in synovial tissues in a dose manner. **Conclusion:** Anti-inflammatory effects of emodin against collagen-induced arthritis in mice may be due to its ability to inhibit pro-inflammatory mediators. Emodin may be a promising potential therapeutic reagent for arthritis treatment^[21].

Systemic lupus erythematosus (SLE) is an autoimmune connective-tissue disease, predominantly affecting females aged between their late teens and early 40s, has a wide range of clinical features. Active P-glycoprotein (P-gp) molecules have been shown to transport steroids out of peripheral lymphocytes, resulting in poor responses to systemic steroid therapy in patients with SLE. The authors investigated the correlation between the expression or activity of P-gp in peripheral lymphocytes and disease control in SLE patients with a long history of systemic steroid treatment. A total of 60 SLE patients who had received systemic steroid treatment for longer than 6 months and 30 healthy subjects were monitored. SLE patients were subclassified into those with active and severely forms of the disease according to their disease activity (estimated by SLE Disease Activity Index-2000). The expression levels and activity of P-gp in peripheral blood lymphocytes were determined. Lymphocytes, obtained from three patients with severely active SLE, with high levels of P-gp expression were treated with cyclophosphamide, mycophenolic acid or emodin *in vitro* and Rh123-efflux activity was measured. P-gp expression in the peripheral lymphocytes of the SLE patients was significantly higher compared with that of the healthy controls, and a positive correlation between disease activity and P-gp expression levels was observed in these 60 patients. A significant increase in P-gp expression was observed in the severely active compared with the active SLE group. Treatment of lymphocytes with 100 μ M cyclophosphamide or 100 μ M emodin *in vitro* induced up to a 2-fold increase in the mean fluorescence intensity, as detected by the Rh123-efflux assay. In conclusion, the high expression levels of P-gp in the peripheral lymphocytes of SLE patients leads to poor disease control by systemic steroids. Emodin possesses a promising effect for overcoming P-gp-mediated steroid resistance by inhibiting the P-gp efflux function^[22].

Emodin has been identified to have the potential to improve lung fibrosis and lung cancer. To avoid the liver and kidney toxicities and the fast metabolism of emodin, emodin-loaded polylactic acid microspheres (ED-PLA-MS) were prepared and their characteristics were studied. ED-PLA-MS were prepared by the organic phase

dispersion-solvent diffusion method. By applying an orthogonal design, the results indicated that the optimal formulation was 12 mg/mL PLA, 0.5% gelatin, and an organic phase: glycerol ratio of 1:20. Using the optional experimental conditions, the drug loading and encapsulation efficiencies were $(19.0 \pm 1.8)\%$ and $(62.3 \pm 2.6)\%$, respectively. The average particle size was $9.7 \pm 0.7 \mu\text{m}$. *In vitro* studies indicated that the ED-PLA-MS demonstrated a well-sustained release efficacy. The microspheres delivered emodin, primarily to the lungs of mice, upon intravenous injection. It was also detected by microscopy that partial lung inflammation was observed in lung tissues and no pathological changes were found in other tissues of the ED-PLA-MS-treated animals. These results suggest that ED-PLA-MS are of potential value in treating lung diseases in animals^[23].

POTENTIAL THERAPEUTIC BENEFITS OF ALOE VERA IN TREATMENT OF RHEUMATOID ARTHRITIS

The authors examined the anti-inflammatory activity of *Aloe vera* inner leaf gel component. A simple *in vitro* assay was used to determine the effect of the gel on bacterial-induced TNF- α and IL-1 β concentrations. The organism used for evaluation was *Shigella flexneri*, as this is a significant world-wide causative agent of gastrointestinal disease. In addition, bacterial lipopolysaccharide was examined. The results showed that these pro-inflammatory cytokines were suppressed to significant ($p < 0.05$) levels using 45 mg/ml freeze-dried inner gel. The action of *Aloe vera* differed from a non-steroid anti-inflammatory drug (ibuprofen), which caused a significant increase ($p < 0.05$) in TNF- α and IL-1 β production^[24].

An expanding spectrum of acute and chronic non-infectious inflammatory diseases is uniquely responsive to IL-1 β neutralization. IL-1 β mediated diseases are often called "auto-inflammatory" and the dominant finding is the release of the active form of IL-1 β driven by endogenous molecules acting on the monocyte/macrophage. IL-1 β activity is tightly controlled and requires the conversion of the primary transcript, the inactive IL-1 β precursor, to the active cytokine by limited proteolysis. Limited proteolysis can take place extracellularly by serine proteases, released in particular by infiltrating neutrophils or intracellularly by the cysteine proteases caspase-1. Therefore, blocking IL-1 β resolves inflammation regardless of how the cytokine is released from the cell or how the precursor is cleaved. Evidence for the involvement of IL-1 β and the clinical results of reducing IL-1 β activity in this broad spectrum of inflammatory diseases are focused in the present review^[25].

Aloe vera contains various carbohydrate polymers, notably glucomannans, along with a range of other organic and inorganic components. Phenolic compounds have been identified as far as chromones, anthraquinones or anthrone derivatives. Three distinct preparations of aloe plants are mostly used in medicinal practices that are quite different in their chemical composition and their therapeutic properties, aloe latex; aloe gel; and aloe whole leaf (aloe extract). Aloe latex is used for its laxative effect; aloe gel is used topically for skin ailments, such as wound healing, psoriasis, genital herpes and internally by oral administration in diabetic and hyperlipidaemic patients and to heal gastric ulcers; and aloe extract is potentially useful for cancer and AIDS. *Aloe vera* possesses several pharmacological properties such as promoting and healing wound and burn, frost-bite healing, with addition to having anti-inflammatory, antifungal, hypoglycemic and gastroprotective properties. The authors explored the phytochemical and pharmacological knowledge

as well as several promising aspect for research on aloe^[26].

The authors aimed to determine the effect of *Aloe vera* on the molecular mechanisms of NOD-like receptor family pyrin domain-containing 3 (Nlrp3) inflammasome-mediated IL-1 β production in LPS-activated human THP-1 cells and monocyte-derived macrophages. **Results:** *Aloe vera* significantly reduced IL-8, TNF α , IL-6 and IL-1 β cytokine production in a dose dependent manner. The inhibitory effect was substantially more pronounced in the primary cells. The authors found that *Aloe vera* inhibited the expression of pro-IL-1 β , Nlrp3, caspase-1 as well as that of the P2X purinergic receptor 7 (P2X7R) in the LPS-induced primary macrophages. Furthermore, LPS-induced activation of signaling pathway like NF- κ B, p38, JUK and ERK were inhibited by *Aloe vera* in these cells. **Conclusion:** The authors show for the first time that *Aloe vera*-mediated strong reduction of IL-1 β appears to be the consequence of the reduced expression of both pro-IL-1 β as well as Nlrp3 inflammasome components via suppressing specific signal transduction pathways. Furthermore, the authors show that the expression of the ATP sensor P2X7R is also downregulated by *Aloe vera* that could also contribute to the attenuated IL-1 β cytokine secretion. These results may provide a new therapeutic approach to regulate inflammasome-mediated responses^[27].

Rheumatoid arthritis (RA) is an autoimmune disease characterized with a chronic, systemic inflammation which primary affects synovial joints. A good number of anti-inflammatory or immunomodulatory plant extracts (and phytochemicals thereof) seem to exist whilst several of them have been specially studied in the context of RA. One of potential example in this regard includes *Aloe vera*. Over 75 active components have already been identified in *Aloe vera* leaf gels and some of them have been implicated as immunomodulatory compounds and as such beneficial against RA, based on animal studies. From that view point, *Aloe vera* and its phytochemical constituents have the potential for further studies leading to newer and more efficacious drugs against rheumatoid arthritis^[28].

The authors investigated the effects of *Aloe vera* gel and *Aloe vera* gel constituents on the activity of microbial and human metalloproteinases. *Clostridium histolyticum collagenase* (ChC) resulted dose-dependently inhibited by aloe gel and the activity-guided fractionation led to an active fraction enriched in phenolics and aloins. Aloins have been shown to be able to bind and to inhibit ChC reversibly and non-competitively. Aloe gel and aloins are also effective inhibitors of stimulated granulocyte matrix metalloproteinases (MMPs). The remarkable structural resemblances between aloins and the pharmacophore structure of inhibitory tetracyclines, suggest that the inhibitory effects of aloins are via an interaction between the carbonyl group at C₉ and adjacent hydroxyl group of anthrone (C₁ or C₈) at the secondary binding site of enzyme, destabilizing the structure of granulocyte MMPs^[29].

The authors demonstrated that aloe emodin dose-dependently inhibited inducible nitric oxide synthase (iNOS) mRNA expression and nitric oxide (NO) production at 5-40 μM . In addition, the levels of cyclooxygenase-2 (COX-2) mRNA and prostaglandin E₂ (PGE₂) production were suppressed by 40 μM aloe emodin. Aloe also suppressed the production of NO at 5-40 μM , although it did not suppress PGE₂ production. The present results indicate that aloe and aloe emodin possibly suppress the inflammatory responses by blocking iNOS and COX-2 mRNA expression. The anti-inflammatory effect of aloe emodin was comparable to that of kaempferol and quercetin, indicating aloe emodin as a possible key constituent responsible for the anti-inflammatory activity of aloe^[30].

The authors investigated the anti-inflammatory effects of

aloe emodin and the molecular mechanism involved in its anti-inflammatory effects. **Methods:** RAW264.7 cells were stimulated by lipopolysaccharide (LPS) in the presence or absence of aloe emodin. The proliferation of RAW264.7 cells was assayed by the Alamar-blue method. The quantity of NO was determined by Griess assay. The expression of pro-inflammatory cytokines was determined by enzyme-linked immunosorbent assay and quantitative real-time PCR. Inducible iNOS, inhibitor of nuclear factor κ B ($\text{I}\kappa\text{B}\alpha$), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), c-Jun NH2-terminal kinase (JNK), and Akt/phosphoinositide 3-kinase (PI3K) protein expression levels were determined by western blotting. **Results:** Aloe emodin markedly suppressed the production of NO, IL-6, and IL-1 β in LPS-stimulated RAW264.7 cells with no apparent cytotoxicity. The mRNA expression levels of iNOS, IL-6 and IL-1 β genes were also significantly inhibited by aloe emodin. Western blot analysis showed that aloe emodin suppressed LPS-induced iNOS protein expression, $\text{I}\kappa\text{B}\alpha$ degradation, and the phosphorylation of ERK, p38, JNK and Akt. **Conclusions:** These results demonstrated that aloe emodin is the bioactive component conferring an anti-inflammatory effect through a likely mechanism involving a decrease in pro-inflammatory cytokin production in LPS-induced RAW264.7 macrophages via inhibition of NF- κ B, MAPK, and PI3K pathways^[31].

A series of aloe emodin derivatives were synthesized and evaluated as xanthine oxidase (XO) inhibitors. Among them, four aloe emodin derivatives showed significant inhibitory activities against XO. The compound, primary alcohol group at C2 in aloe emodin was substituted to formyl group (A1), possessed the best XO inhibitory activity with IC_{50} of 2.79 μM . Lineweaver-Burk plot analysis revealed that A1 acted as a mixed-type inhibitor for XO. The docking study revealed that the molecule A1 had strong interactions with the active site of XO and this result was in agreement with kinetic study. The 4,5-hydroxyl groups and the formyl group at C2 of A1 could interact with the xanthine-binding site of XO. The free 4,5-hydroxyl groups and the formyl group of at C2 of A1 played significant roles for the XO inhibition activity. Compound A1 is a new-type candidate for further development for the treatment of gout^[32].

The authors investigated the inhibitory mechanism of anthraquinone derivatives like aloe-emodin, emodin and chrysophanol, against influenza A virus. Aloe emodin with a lower cytotoxicity showed concentration-dependently reducing virus-induced cytopathic effect and inhibiting replication of influenza A in MDCK cells. 50% inhibitory concentration value of aloe emodin on virus yield was less than 0.05 $\mu\text{g}/\text{mL}$. Proteomics and Western blot of MDCK cells indicated aloe emodin up-regulating galectin-3, and thioredoxin as well as down-regulating nucleoside diphosphate kinase A. Western blot and quantitative PCR confirmed aloe emodin up-regulating galectin-3 expression; recombinant galectin-3 augmented expression of antiviral genes IFN- β/τ , RNA-dependent protein kinase (PKR) and 2',5'-oligoadenylate synthase (OAS) in infected cells, agreeing with expression pattern of those treated with aloe emodin. Galectin-3 also inhibited influenza A virus replication. Proteomic analysis of treated cells indicated galectin-3 up-regulation as one anti-influenza A virus action by aloe emodin. Since galectin-3 exhibited cytokine-like regulatory actions via JAK/STAT pathways, aloe emodin also resorted NS1-inhibited STAT-1 mediated antiviral response in transfected cells: e.g., STAT 1 phosphorylation of interferon stimulator response element-driven promoter, PKR and 2',5'-OAS expression. Treatment with aloe emodin could control influenza infection in human^[33].

Rheumatoid arthritis (RA) is a complex and common systemic

autoimmune disease characterized by synovial inflammation and hyperplasia. Galectins are potent immune regulators and modulate a range of pathological processes, such as inflammation, autoimmunity, and cancer. The authors reviewed accumulated evidence showing that several family members of galectins play positive or negative roles in the disease development of RA, through their effects on T and B lymphocytes, myeloid lineage cells, and fibroblast-like synoviocytes. The authors summarized the function of different galectins in immune modification and their distinct roles in RA pathogenesis^[34].

Acemannan has been known to have antiviral and antitumoral activities *in vivo* through activation of immune responses. The authors investigated the present study to define the immunomodulatory activity of acemannan on dendritic cells (DCs), which are the most important accessory cells for initiation of primary immune responses. Immature DCs were generated from mouse bone marrow (BM) cells by culturing in a medium supplemented with granulocyte/macrophage-colony stimulating factor and IL-4, and then stimulated with acemannan, sulfated acemannan, and LPS, respectively. The resultant DCs were examined for phenotypic and functional properties. Phenotypic analysis for the expression of class II MHC molecules and major co-stimulatory molecules such as B7-1, B7-2, CD40 and CD54 confirmed that acemannan could induce maturation of immature DCs. Functional maturation of immature DCs was supported by increased allogeneic mixed lymphocyte reaction and IL-12 production. The differentiation-inducing activity of acemannan was almost completely abolished by chemical sulfation. Based on these results, the authors proposed that the adjuvant activity of acemannan is at least in part due to its capacity to promote differentiation of immature DCs^[35].

The authors hypothesized acemannan could affect bone formation. Primary rat bone marrow stromal cells (BMSCs) were treated with various concentrations of acemannan. New DNA synthesis, VEGF, BMP-2, alkaline phosphatase activity, bone sialoprotein, osteopontin expression, and mineralization were determined by 3H-thymidine incorporation assay, ELISA, biochemical assay, western blotting, and alizarin red staining, respectively. In an animal study, mandibular right incisors of male Sprague-Dawley rats were extracted and an acemannan treated sponge was placed in the socket. After 1, 2, and 4 weeks, the mandibles were dissected. Bone formation was evaluated by dual-energy X-ray absorptiometry and histopathological examination. The *in vitro* results revealed acemannan significantly increased BMSC proliferation, VEGF, BMP-2, alkaline phosphatase activity, bone sialoprotein and osteopontin expression, and mineralization. *In vivo* results showed acemannan-treated groups had higher bone mineral density and faster bone healing compared with untreated controls. A substantial ingrowth of bone trabeculae was observed in acemannan-treated groups. These data suggest acemannan could function as a bioactive molecule inducing bone formation by stimulating BMSCs proliferation, differentiation into osteoblasts, and extracellular matrix synthesis. Acemannan could be a candidate natural biomaterial for bone regeneration^[36].

A complete chemical characterisation of *Aloe vera* plant was carried out from the dissection of the plant whole leaves in fillets and skin. In addition, a mucilaginous gel from the fillets was also characterised. Extraction with ethanol of lyophilised aloe fraction (alcohol insoluble residues: AIRs) allowed to concentrate the major fraction composed of carbohydrates up to 80%. The composition of the main type of polysaccharides present in the aloe AIRs was determined. Mannose and cellulosic glucose were the major polysaccharide components in all AIRs, significant amounts of pectic polysaccharides were also detected. Sequential extraction of

polysaccharides present in *Aloe vera* plant portions, revealed that two main types of mannose-containing polymers were present in the *Aloe vera* plant. The polysaccharide detected in the fillet and in the gel fractions corresponded to a storage polysaccharide located within the protoplast of the parenchymatous cells. Its structural and compositional features corresponded to the active polysaccharide known as acemannan. On the contrary, in the skin tissue, the mannosy residues arose from a structural polysaccharide located within the cell wall matrix. Structural and compositional differences between both polymers were confirmed by methylation analysis. The fact that acemannan is a reserve polysaccharide might help to explain most of the compositional variations reported in the literature for *Aloe vera* carbohydrates. Further, sequential extraction was shown to identify several pectic polysaccharides, rich in uronic acids, with a composition similar to that of several antitumoral polymers found in different plant tissues. The investigation provided a better understanding of the main compositional and structural features of *Aloe vera* cell walls, and also of the origin of a non-cell wall polysaccharide, acemannan^[37].

The clear pulp of *Aloe vera* leaf is widely used in various medical, cosmetic and nutraceutical applications. Many beneficial effects of this plant have been attributed to the polysaccharides present in the pulp. However, discrepancies exist regarding the composition of pulp polysaccharide species and an understanding of pulp structure in relation to its chemical composition has been lacking. Thus, the authors examined pulp structure, isolated structural components and determined their carbohydrate compositions along with analyzing a partially purified pulp-based product. Light and electron microscopy showed that the pulp consisted of large clear mesophyll cells with a diameter as large as 1,000 microm. These cells were composed of cell walls and cell membranes along with a very limited number of degenerated cellular organelles. No intact cellular organelles were found in mesophyll cells. Following disruption of pulp by homogenization, three components were isolated by sequential centrifugation with low-to-high speed. They were thin clear sheets, microparticles and a viscous liquid gel, which corresponded to cell wall, degenerated cellular organelles and liquid content of mesophyll cells based on morphological and chemical analysis. These three components accounted for 16.2% (± 3.8), 0.7% (± 0) and 83.1% (± 0) of the pulp on a dry weight basis. The carbohydrate composition of each component was distinct; liquid gel contained mannan, microparticles contained galactose-rich polysaccharide(s) and cell walls contained an unusually high level of galacturonic acid (34%, w/w; Gal A). The high Gal A level in the cell wall suggests a very high content of pectic substance or pectin. The same three components were also found in acemannan hydrogel with mannan as the predominant component. Thus, different pulp structural components are associated with different polysaccharides and thus may potentially be different functionally. Thus, the pulp contains all three polysaccharides and they may be isolated together or individually dependent on the processing methods used. These findings may help lay a basis for further studies and development of better controlled processing methods and applications for this well-accepted medicinal plant^[38].

THE EFFICACY OF A DIETARY PLANT-DERIVED POLYSACCHARIDE SUPPLEMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

The authors hypothesized that a small subset of colonic flora would

be able to utilize complex plant polysaccharides (CPPs). Feces from 4 healthy humans were sequentially passed three times over 9 days in growth media composed of either *Aloe vera* gel polysaccharides (AVP), larch arabinogalactan (LAG), or a dietary supplement including these two ingredients suspended in a minimal salt solution. CPPs were first dialyzed to eliminate polymers and sugars <8,000 MW, forcing bacteria to consume only higher MW components. Isolates were obtained on rich media and then 16S rDNA sequenced for species identification. API 50CH strips were in some cases used to confirm identification. A total of 6 species were identified; however, 90% of isolates were *Enterococci*. Supernatant analysis showed variable consumption of the entire MW range of polysaccharide components. These findings suggest that *Enterococcus* species play an important role in the utilization of CPPs^[39].

Dramatic changes in socioeconomic status, cultural traditions, population growth, and agriculture are affecting diets worldwide. Understanding how our diet and nutritional status influence the composition and dynamic operations of our gut microbial communities, and the innate and adaptive arms of our immune system, represents an area of scientific need, opportunity and challenge. The insight gleaned should help address a number of pressing global health problems. The authors expressed a schematic of envisioned interrelationships between the gut microbiota, the immune system and diet that underlies the development of malnutrition, and metabolic sensors that help co-ordinate immune responses^[40].

There is increased interest in the potential benefits of complementary therapies, of which dietary plant-derived polysaccharides (dPPs) are an important component. The authors examined the impact of oral ingestion of a pre-biotic dPPs supplement active compound (AC) on serum glycosylation and clinical variables associated with inflammation and general health in patients with rheumatoid arthritis (RA). **Methods:** A double-blind, placebo-controlled, parallel-group clinical trial was used. Participants were randomly assigned to receive AC ($n=33$) or placebo ($n=36$) for 6 months. Serum protein N-glycosylation was determined by mass spectrometry. Patient outcomes were assessed by validated clinical trial health questionnaires. The primary clinical efficacy variable was disease activity score in 28 joints (DAS-28) calculator for RA. **Results:** The groups had comparable baseline-clinical characteristics. AC was well tolerated with low drop-out rates. Supplementation resulted in a 12% significant drop in the level of the agalactosylated (G0F) glycans [8.10 (0.89) to 7.16 (0.60); $p=0.03$], but had no significant overall effect on patient outcomes. The placebo-treated group showed no change in G0F but exhibited a reduction in the levels of fully digalactosylated (G2) glycans (11%; $p=0.03$). Although not clinically significant, DAS scores were, however, marginally lower in the placebo group [difference=0.63 (0.23) S.E.; 95% CI 0.17, 1.10; $p=0.009$] as were two of the secondary variables. **Conclusion:** Short-term dietary supplementation with AC resulted in a moderate, but significant, reduction in G0F levels, but did not result in any clinically significant improvement in disease activity when assessing the study group as a whole. **Rheumatology key messages:** The AC was Ambrotose Complex, a dietary supplement approved as a source of dietary fibre by the Dietary Supplement Standard. AC is a dPP containing a standardized mixture of partially purified saccharides biopolymers, including rich starch. The main active ingredients in AC are *Aloe vera* gel extract, arabinogalactan, gum ghatti, gum tragacanthi and glucosamine. AC supplementation did not result in any clinically significant improvement in RA disease activity. AC supplementation did, however, result in a minor, but significant drop

in hypogalactosylated, G0F, glycans, high levels of which are a well-established feature of active RA^[41].

Extraction, purification, and gel preparation of *Aloe vera* pectin and the evaluation of the biocompatibility of the pectin gels were studied, considering as end use as implantable materials for regenerative medicine. Changing the experimental conditions resulted in four different extraction processes and products with different physical and chemical characteristics. The optimal extraction resulted to be the process: with enzymatic deactivation by microwave and the use of sodium citrate as chelating agent the molecular weight of the pectin extracted was estimated to be 118 kDa and the 2.93% esterification degree. Cytocompatibility of pectin gels, prepared by inotropic gelation, showing an improved cell adhesion if compared to commercial pectin. The results suggest that the extracted *Aloe vera* pectins possess interesting properties to be exploited for the production of mechanically stable gels by inotropic gelation and high rhamnose content matrices for application in regenerative medicine^[42].

EFFICACY OF ALOE VERA IN THE INFLAMMATION OF PATIENTS WITH MILD ULCERATIVE COLITIS

The cause of irritable bowel syndrome (IBS) is unknown. It may follow gastroenteritis and be associated with an abnormal gut flora and with food intolerance. The authors designed to assess whether these factors were associated with colonic malfermentation. **Interpretation:** Colonic-gas production, particularly H₂, is greater in patients with IBS than in controls, and both symptoms and gas production are reduced by an exclusion diet. This reduction may be associated with alterations in the activity of hydrogen consuming bacteria^[43].

The authors aimed to assess the effects of *Aloe vera* in vitro on production of reactive oxygen metabolites, eicosanoids and interleukin-8 (IL-8), all of which may be pathogenic in inflammatory bowel disease. **Methods:** The anti-oxidant activity of *Aloe vera* was assessed in two cell-free, radical-generating systems and by the chemiluminescence of incubated colorectal mucosal biopsies.

Eicosanoid production by biopsies and IL-8 release by CaCo2 epithelial cells in the presence of *Aloe vera* were measured by enzyme-linked immunosorbent assay. **Results:** *Aloe vera* gel had a dose-dependent inhibitory effect on reactive oxygen metabolite production; 50% inhibition occurred at 1 in 1000 dilution in the phycoerythrin assay and at 1 in 10-50 dilution with biopsies. *Aloe vera* inhibited the production of prostaglandin E₂ by 30% at 1 in 50 dilution ($p=0.03$), but had no effect on thromboxane B₂ production. The release of IL-8 by CaCo2 cells fell by 20% ($p<0.05$) with *Aloe vera* diluted at 1 in 100, but not at 1 in 10 or 1 in 1000 dilutions. **Conclusion:** The anti-inflammatory actions of *Aloe vera* gel in vitro provide support for the proposal that it may have a therapeutic effect in inflammatory bowel disease^[44].

The authors aimed to perform a double-blind, randomized, placebo-controlled trial of the efficacy and safety of *Aloe vera* gel for the treatment of mildly to moderately active ulcerative colitis. **Methods:** Forty-four evaluable hospital out-patients were randomly given oral *Aloe vera* gel or placebo, 100 mL twice daily for 4 weeks, in a 2:1 ratio. The primary outcome measures were clinical remission (Simple Clinical Colitis Activity Index ≤ 2), sigmoidoscopic remission (Baron score ≤ 1) and histological remission (Saverymuttu score ≤ 1). Secondary outcome measures included changes in the

Simple Clinical Colitis Activity Index (improvement was defined as a decrease of ≥ 3 points: response was defined as remission or improvement), Baron score, histology score, haemoglobin, platelet count, erythrocyte sedimentation rate, C-reactive protein and albumin. **Results:** Clinical remission, improvement and response occurred in nine (30%), 11 (37%) and 14 (47%), respectively, of 30 patients given *Aloe vera*, compared with one (7%) [$p=0.09$; odds ratio, 5.6 (0.6-49)], one (7%) [$p=0.06$; odds ratio, 7.5 (0.9-66)] and two (14%) [$p<0.05$; odds ratio, 5.3 (1.0-27)], respectively, of 14 patients taking placebo. The Simple Clinical Colitis Activity Index and histological scores decreased significantly during treatment with *Aloe vera* ($p=0.01$ and $p=0.03$, respectively), but not with placebo. Sigmoidoscopic scores and laboratory variables showed no significant differences between *Aloe vera* and placebo. Adverse events were minor and similar in both groups of patients. **Conclusion:** Oral *Aloe vera* taken for 4 weeks produced a clinical response more often than placebo: it also reduced the histological disease activity and appeared to be safe. Further evaluation of the therapeutic potential of *Aloe vera* gel in inflammatory bowel disease is needed^[45].

The authors aimed to assess the efficacy of *Aloe vera* on irritable bowel syndrome (IBS) in refractory secondary care patients. Patients with IBS were randomized to receive *Aloe vera* or matching placebo for a month. Symptoms were assessed at baseline, 1 and 3 months. Fifty eight patients randomized, 49 completed the protocol to 1 month and 41 to 3 months. Eleven of thirty-one (35%) *Aloe vera* patients, and 6 of 27 (22%) placebo patients responded at 1 month ($p=0.763$). Diarrhoea predominant patients showed a trend towards a response to treatment at 1 month (10/23 versus 2/14, $p=0.07$). There was no evidence that *Aloe vera* benefits patients with IBS. However, the authors could not rule out the possibility that improvement occurred in patients with diarrhoea or alternating IBS whilst taking *Aloe vera*. Further investigations are warranted in patients with diarrhoea predominant IBS, in a less complex group of patients^[46].

The authors investigated 33 patients consecutively attending their clinic with constipation- predominated refractory IBS into an 8 week treatment course with *Aloe vera* including a weekly follow-up for evaluating treatment efficacy; and in each session, a new *Aloe vera* bottle would be given to patients. *Aloe vera* juice was administered 30 ml twice daily. Visual analog scale (100 mm) questionnaires were used on a daily schedule to assess the variables. The mean \pm SD of pain/discomfort at baseline level was 4.2 \pm 0.8, which decreased to 0.3 \pm 0.6 at the end of the study ($p<0.001$). The mean \pm SD of flatulence decreased from 3.7 \pm 1.2 at baseline to 0.3 \pm 0.6 at the end of the study ($p<0.001$). Stool consistency, urgency, and frequency defecation ($p>0.5$ in all) reacted not to *Aloe vera* therapy. Potential criticism may arise over the study's methodology. The first and most important thing is that the trial was not placebo-controlled. Since placebo has been proved to have symptom-relieving effects on IBS, interpretation of the study findings, without comparing them to placebo treated patients can raise controversial debates. "Refractory" IBS was defined when patients were not satisfied with their current treatment. On the other hand, the study has several powerful points. First of all, the authors separately surveyed symptoms of the patients one by one based on self-rated scales; however, in most previous study evaluated by quality of life questionnaires, which are not specific to IBS, and does not show the distinct impact of *Aloe vera* on patients complaints. To their knowledge, it is the first study using self-rated questionnaires that shows *Aloe vera* can reduce pain/discomfort of patients with IBS. In a previous study, Odes and Madar failed to find any association between *Aloe vera* use and pain reduction in patients complaining constipation. Moreover, Hutchings *et al* and Davis *et*

al also found no beneficial effect for *Aloe vera* on IBS symptoms. In conclusion, *Aloe vera* can reduce abdominal pain/discomfort as well as flatulence in patients with constipation predominated IBS while it is unable to improve urgency and frequency as well as consistency of stool in these patients. Further, placebo-controlled studies with larger patient population are needed to confirm the results^[47].

The ulcerative colitis (UC) belong to the group of diseases called inflammatory bowel disease (IBD) which is characterized by a chronic ulceration of colon. The conventional treatment can have adverse effects and does not guarantee effectiveness in some patients requiring aggressive therapy using adjuvant therapy. *Aloe vera* has been shown to have a beneficial effect in different disease, and have anti-inflammatory effect in UC patients. **Objective:** Measuring the effect of the consumption of 200 mL of *Aloe vera* gel daily for a period of three months, in the degree of inflammation in patients with mild UC based on Mayo scale and quantification of IL-6 in the colonic mucosa. Clinical trials were started under National Institute of Medical Science and Nutrition as follows: Study type: Interventional, Study design: Allocation: Randomized, Endpoint classification: Safety/Efficacy study, Intervention model: Parallel assignment, Masking: Double blind, Primary purpose: Treatment, Study primary completion date: Dec 2013, Estimated study completion date: Dec 2014^[48].

ANTI-INFLAMMATORY PROTEIN AND/OR LECTIN FROM ALOE VERA GEL

The authors aimed to test the therapeutic effect of *Aloe vera* in experimental model of multiple sclerosis (MS). All experiments were conducted on C57BL/6 male mice aged 6-8 weeks. To induce the experimental autoimmune encephalomyelitis (EAE), 250 µg of the myelin oligodendrocyte glycoprotein 35-55 peptide emulsified in complete Freund's adjuvant was injected subcutaneously on day 0 over two flank areas. In addition, 200 ng of pertussis toxin in 100 µL phosphate buffered saline was injected intra-peritoneally on days 0 and 2. The therapeutic protocol was carried out intra-gastrically using 120 mg/kg/day. *Aloe vera* from 7 days before to 21 days after EAE induction. The mice were killed 21 days after EAE induction. The brains of mice were removed for histological analysis and their isolated splenocytes were cultured. The results indicated that treatment with *Aloe vera* caused a significant reduction in severity of the disease in experimental model of MS. Histological analysis showed 3±2 plaques in *Aloe vera*-treated mice compared with 5±1 plaques in control group. The density of mononuclear infiltration in the CNS of *Aloe vera*-treated mice (500±200) was significantly less in comparison to 700±185 cells in control group. Moreover, the serum level of nitric oxide in treatment group was significantly less than control animals. The level of IF- γ in cell culture supernatant of treated mice splenocytes was lower than control group, whereas decrease in serum level of IL-10 in treatment group was not significant in comparison with control mice. These data indicate that *Aloe vera* therapy can attenuate the disease progression in experimental model of MS^[49].

Despite being used as arthritis treatment for centuries, evidence of effectiveness of *Aloe vera* in anecdotal or from small studies on osteoarthritis (OA). The perceived benefits of prescribing *Aloe vera* for OA may be twofold: it has utility as an anti-inflammatory agent and also as a prophylactic against the gastrointestinal irritant effects of non-steroidal anti-inflammatory drugs^[50].

An active glycoprotein fraction containing 58% protein was isolated from *Aloe vera* gel by precipitation with 55% ammonium

sulfate followed by gel permeation using DEAE-Sephacel A-25, Sepharose 6B and Sephadex G-50 columns in a yield of 3×10⁻³%. The glycoprotein fraction showed a single band corresponding to a subunit of verectin^[51] at the same position when stained with both coomassie brilliant blue and periodic acid-schiff reagents on 18% SDS-PAGE. The molecular weight (14 kDa) was confirmed by Sephadex G-50 column chromatography. The glycoprotein fraction showed a radical scavenging activity against superoxide anion generated by the xanthine-xanthine oxidase system as well as inhibition of cyclooxygenase-2 and reduction of thromboxane A₂ synthase level *in vitro*^[52]. In an early study *in vitro* and *in vivo*, the potential anticancer properties and modulatory effect of selected *Aloe vera* active principles on antioxidant enzyme activities were evaluated. Three ingredients, aloesin, aloe emodin, barbaloin and the N-terminal octapeptide (DEDNVLTT) derived from verectin (lectin) and synthesized by Peptide Institute, Japan. The data suggest that four *Aloe vera* compounds may exert their chemo-preventive effect through modulating antioxidant and detoxification enzyme activity levels, as they are one of the indicators of tumorigenesis^[53]. The potential anticancer properties and modulatory effect of *Aloe vera* active principles were evaluated on antioxidant enzyme activity *in vitro* and *in vivo* studies.

The purified aloe protein (14 kD) isolated from *Aloe vera* gel exhibited a potent anti-fungal activity and an anti-inflammatory property against lipoxygenase and cyclooxygenase-2 with 84% and 73% inhibition, respectively, and was verified by binding with the protein by real time method by the phenomenon of surface plasmon resonance. The aloe protein (ASQLNAGQLGGQS) is novel protein possessing antifungal and anti-inflammatory properties^[54].

A protease inhibitor protein with the molecular mass of 11.804 Da (analyzed by matrix assisted laser desorption/ionization time-of-flight mass spectrometry) isolated from *Aloe vera* gel was designated as AVPI-12. The isoelectric point of the protein is about 7.43. The first ten amino acid sequence from the N-terminal was found to be RDWAEPNDGY. The inhibition of the fibrinolytic and fibrinolytic activities of plasmin by AVPI-12 suggests that the inhibitor has potential for use in anti-fibrinolytic treatment^[55]. The fibrinolytic inhibitory activity of AVPI-12 and the small-angle X-ray scattering showed that the protein could protect human fibrin clot from complete degradation by plasmin.

Rheumatoid arthritis is associated with an excessive risk of cardiovascular morbidity and mortality, and inflammation appears to be the missing link explaining this markedly elevated risk. Inflammation is a potent inducer of coagulation and fibrinolysis and may contribute to atherosclerotic and thrombotic components of cardiovascular events. Thrombin-activatable fibrinolysis inhibitor (TAFI), a procarboxypeptidase in plasma, is a regulatory protein of the coagulation/fibrinolysis balance as well as inflammation. TAFI α , the activated form of TAFI acts by removing C-terminal arginine and lysine residues from substrates such as fibrin degradation products, bradykinin and the anaphylatoxins C3a and C5a^[56].

The understanding of cholesterol and its pathogenesis to Alzheimer's disease (AD) pathogenic process is important for the possible prevention of AD. High fibre diets that contain phytosteroids have shown to lower LDL and increase HDL cholesterol and are implicated in membrane cholesterol and amyloid β (A β) homeostasis. The convergence of diet and AD may be related to the effects of phytosterols since plasma cholesterol is closely linked and regulated by phytosterols. Dietary fibre modifications that are low in fat and glucose reduce the risk for AD by not only effecting cell membranes and nutrient sensing G coupled receptors but also by regulating

number of nuclear receptors such as histone deacetylases (HDAC) and peroxisome proliferator activated receptors (PPARs) that control glucose, fatty acids and cholesterol and have significant effects on the brain cholesterol homeostasis and amyloidosis. The peripheral sink A β hypothesis indicates that the peripheral clearance of A β and its regulation by dietary phytosterols is of substantial interest since it may delay hypercholesterolemia and the early onset of amyloid plaque development. Liver disease has been of central importance with aging and programmed cell death pathways. Nutritional therapy has emerged as a novel approach to control appetite and the role of nutrigenomics as an early nutritional therapy may assist genes to delay liver and brain diseases such as Parkinson's disease and Huntington's disease that are associated with aging. The understanding of phytosterols and the role of these lipids in drug therapy such as cholesterol lowering drugs may provide molecular mechanisms that are involved in the regulation of cell A β clearance and metabolism. High fibre diets also contain various fatty acids such as the short chain fatty acids (SCFA) and the understanding of synergistic effects of SCFA and phytosterols in glucose regulation and cholesterol homeostasis important to our understanding of diet, lifestyle and drugs in relation to peripheral amyloidosis and gene expression that play an early role in the development of AD^[57].

Aloe vera at dose of 100 mg and 300mg/kg daily for 4 days blocked the wound healing suppression of hydrocortisone acetate up to 100% using the wound tensile strength assay. This response was because of the growth factors present in *Aloe vera* masking the wound healing inhibitions such as sterols and certain amino acids. The sterols (campesterol, stigmasterol, lupeol, and β -sitosterol) showed good anti-inflammatory activity in reducing the croton oil-induced ear swelling. This activity displayed a dose-response relationship^[58].

CONCLUSION AND FUTURE PERSPECTIVES

Contribution of aloe high molecular weight fraction (AHM) containing acemannan and verectin, as carbohydrate-based adjuvants to immune response was examined in pre-clinical studies and AHM was considered to be a novel low-cost and safe drug of natural origin indicating a possible therapeutic efficacy in prevention of age-related diseases^[59].

Galectins are a group of lectins that bind to β -galactoside carbohydrates on the cell surface and in the extracellular matrix. They are expressed in a wide variety of tissues and organs with the highest expression in the immune system. The direct, dependent link between galectin-3 and numerous acute and chronic disease states is what gives this molecule such as important diagnostic and therapeutic implications, becoming widely accepted in the medical community. Galectin-3 plays a dual role both as a diagnostic marker and an important therapeutic target. Accumulated evidence shows that several family members of galectins play positive or negative roles in the disease development of rheumatoid arthritis, through their effects on T and B lymphocytes, myeloid lineage cells, and fibroblast-like synoviocytes. The authors summarized the function of different galectins in immune modulation and their distinct roles in rheumatoid arthritis pathogenesis^[60].

Pectins are a family of covalently linked galacturonic acid-rich polymers which are found in high amounts in the cell wall of *Aloe vera* plant. The main role of the cell wall components is to give mechanical strength to plants, to maintain an extracellular water phase by imbibition and to provide a barrier from external environment. In human, pectin, as a dietary fiber, is not enzymatically

digested in the small intestine but is degraded by the microbiota in the colon. It keeps its gelling action in the digestive tract, so that it slows down digestion. In addition, several studies have shown that orally taken pectin decreases the risk of intestinal infection and of diarrhea in children by favouring the growth of *Bifidobacteria* and *Lactobacillus* bacterial species in the colon. As a dietary fiber, pectin is not digested in the upper digestive tract but is fermented in the colon by bacteria into butyrate, which inhibits colon inflammation and prevents carcinogenesis. pH-Modified pectin as well as galactan-rich pectin, such as modified citrus pectin (MCP) and aloe pectin, are capable of interacting with galectin-3, thus inhibiting cell-cell interactions and cancer cell metastasis. MCP is rapidly earning esteem as a versatile and important dietary supplement for protecting long-term health^[61]. Aloe pectins having two classes distinguished by size are obtained: the room temperature extraction generated a high-molecular-weight (HMW) pectin whereas extraction with heating produced a low-molecular-weight (LMW) pectin. Aloe pectins naturally have a low methoxyl content. Both the HMW and LMW pectins are capable of gel formation in the presence of calcium. The HMW aloe pectin calcium gel is a highly efficient encapsulating agent suitable for controlled release of pharmacological substances, such as proteins, antibodies, and vaccines. Aloe pectins form a matrix for antigen and antibody precipitation reactions and a storage matrix for pharmacological substances^[38]. *Aloe vera* inner gel is used in various medical cosmetic and nutraceutical applications. Many beneficial effects of this plant have been attributed to the polysaccharides present in the pulp. However, discrepancies exist regarding the composition of pulp polysaccharides species, such as acemannan and aloe pectins. These findings may help lay a basis for further therapeutic studies into the biology and development of applications for well-accepted medicinal plant, *Aloe vera*.

The authors showed pectin as one of dietary bioactive compounds thought to be effective in the treatment of cancers. Galectin-3 has been demonstrated in rheumatoid arthritis patients to advance the transformation of synovial fluid into fibrotic tissue, in addition to activating osteoclasts, producing severe debilitation in patients. MCP is rich in β -galactose, giving it the mechanism to attach to the β -galactoside binding protein galectin-3, thus binding and blocking galectin-3 mediated interactions. MCP is therapeutically significant proven natural inhibitor of galectin-3, helping to control cancer development and metastasis, and reducing inflammation and fibrosis throughout the body. MCP can target multiple critical rate-limiting steps involved in cancer and metastasis^[62].

The anti-inflammatory effects of emodin, in vitro and in vivo study, drew the attention and the therapeutic potential of emodin in the treatment and prevention of various inflammatory disorders; pancreatitis, asthma, arthritis, atherosclerosis, myocarditis, glomerulonephritis, rheumatoid arthritis, and Alzheimer's diseases. Emodin strongly inhibited several kinases, such as Her-2/neu, CKII and PKC. It affects NF- κ B, STAT3, AKT, MMPs and Bax/Bcl-2 signaling pathways. Novel molecular targets of emodin identified in last few years have begun to reveal additional therapeutic uses of emodin. Proteomics and western blot of MDCK cells indicated aloe emodin up-regulating galectin-3. Western blot and quantitative PCR confirmed aloe emodin up-regulating galectin-3 expression; recombinant galectin-3 augmented expression of antiviral genes IFN- β , IFN- γ , etc. in infected cells, agreeing with expression pattern of those treated with aloe emodin. Rheumatoid arthritis (RA) is considered as a chronic multi-system autoimmune disease in which various joints in body are affected. Some of the discussed phytochemicals presented in *Aloe vera* could provide relief to RA

patients through promoting wound healing, as well as reducing inflammation and relieving pain, which are common symptoms of RA-affected patients. Dietary intake of non-starch polysaccharide, such as aloe pectin in aloe supplement may reduce an inflammatory disease risk through effects of gut microbiota on nutrient processing and absorption, and on immune function. Pectin and pH- or heat-modified pectin are capable of interacting with galectin-3, thus inhibiting cell-cell interactions and cancer cell metastasis. Hence, more work needs to be done to fully translate the observed pre-clinical findings with the natural agent, such as emodin, aloe emodin, and aloe pectin in well designed clinical trials, especially if used in combination with more conventional molecules.

The human intestinal tract harbors a complex ecosystem of commensal bacteria that play a fundamental role in the well-being of their host. There is a general consensus that diet rich in plant-based foods has many advantages in relation to the health and well-being of an individual. There is a growing understanding of the mechanisms by which the influence of the microbiota projects beyond sites of primary mucosal occupation to other human body systems. Bacteria present in the intestinal tract exert a profound effect on the host immune system, both locally and at distant sites. The oral cavity has its own characteristic microbiota, which concentrates in periodontal tissues and is in close association with a permeable epithelium.

The authors examined evidence which supports a role for the microbiome in the etiology of rheumatic disease. They also discussed how changes in the composition of the microbiota, particularly within the gastrointestinal tract, may be affected by genetics, diet, and use of antimicrobial agents. Evidence was presented to support the theory that an altered microbiota is a factor in the initiation and perpetuation of inflammatory diseases, including rheumatoid arthritis, spondyloarthritis, and inflammatory bowel disease. Mechanisms through which the microbiota may be involved in the pathogenesis of these diseases include altered epithelial and mucosal permeability, loss of immune tolerance to components of the indigenous microbiota, and trafficking of both activated immune cells and antigenic material to the joints. The potential to manipulate the microbiome, by application of probiotics and fecal microbial transplant, is now being investigated. Both approaches are in their infancy with regard to management of rheumatic disease but their potential is worthy of consideration, given the need for novel therapeutic approaches, and the emerging recognition of the importance of microbial interactions with human hosts^[63].

It is now generally accepted that the "central genomic dogma"; a causal chain going from DNA to RNA to proteins and downstream to biological functions, should be replaced by the "fluid genome dogma", that is, complex feed-forward and feed-back cycles that interconnect organism and environment by epigenomic programming- and reprogramming- throughout life and at all levels, sometimes also down the generations. The epigenomic programming is the net sum of interactions derived from own metabolism and microbiota as well as external factors such as diet, pharmaceuticals, environmental compounds. In laboratory animals, it is well established that probiotics can perform epigenomic programming and some results indicated that this is the case also in humans, focusing on foods to pregnant women and infants and in these fields, much attention have been paid to probiotic concept. To date, there is rapidly increasing evidence for host-microbe interaction at virtually all levels of complexity, ranging cell-to-cell communication to extensive systemic signalling. Further, it is a growing body of results indicating that many chronic metabolic and degenerative disorders and diseases-often called 'civilization diseases'-are initiated and/or influenced upon

by non-optimal epigenomic programming, often taking place early in life; the first day of 1,000 days of life-from conception into early infancy-is often called the most important period of life. Breeding counts more than birth. Thomas Edison said that the doctor of the future will no longer treat the human frame with drugs, but rather will cure and prevent disease with nutrition. Dietary modulation to manipulate specific gut microbial species or groups of species may offer new therapeutic approaches to conditions that are prevalent in modern society, such as functional gastrointestinal disorders, obesity and age-related nutritional deficiency.

In present review, the author aimed at reviewing the beneficial prophylactic role of *Aloe vera* as an immunomodulator in rheumatoid arthritis and related complications.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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