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REVIEW

## Removal, Bioleaching and Detoxification of Heavy Metals by Aloe vera as Phytoremediation Case Report: Suppression of Gall Bladder Hypertrophy and Ureteral Stone

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### ABSTRACT

Decontamination of air, soil, and water polluted with dangerous mercury, cadmium, arsenic, and chromium by plants is called phytoremediation. As a living plant, *Aloe vera* was used to clean up the soil, water and air contaminated with dangerous heavy metals and gas. *Aloe vera* plant and the waste powder occurred from aloe vera gel processing, were applied for phytoremediation in which *Aloe vera* was proposed as a cost-effective plant-based approach of

environmental remediation. Bioleaching is a process of extracting metals from their ores through the use of living microorganisms. Endophytic bacteria in *Aloe vera* gel could be used as bioleaching of heavy metals. Furthermore the detoxification of heavy metals and hepato-therapeutic effects by *Aloe vera* was focused specially on hepatic fibrosis and chronic kidney diseases. Case reports showed the suppression of gall bladder hypertrophy and ureteral stone by aloe vera supplements.

**Key words:** Aloe vera and its waste; Removal; Bioleaching; Detoxification; Heavy metals; SO<sub>2</sub> gas; Hepatoprotective effect; Hyaluronan; Case reports; Removal of gall bladder hypertrophy and kidney stone

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### INTRODUCTION

Industrial activities have contributed to inversed levels of contaminants in the environment. Industrialization in manufacturing enterprises has introduced dangerous metals in the environment. Dangerous metals remain in the environment and leave the environment and organisms to continuous risks. Micro-organisms and plants have taken different moving to treat with the harmful effects of these metals<sup>[1]</sup>. One of the strategies is biosorption; the process whereby substances are absorbed by the tissue and organs of organisms. Biosorption is binding of metal ions binding proteins present on the cell wall and absorbing several elements from soil, knowing to have biological functions or toxicity at low concentrations. Biosorption is defined as ability of biological materials to accumulate heavy metals from wastewater. Bioleaching

is a set of actions to percolate metals from their ores through the micro-organisms usage. Endophytic bacteria in Aloe vera gel could be used as bioleaching of heavy metals.

Currently, the industrial and domestic effluents, as well as application of pesticides/herbicides to crop fields have led to the deterioration of environmental quality. Among these pollutants, heavy metals represent a special group because they are not chemically and biologically degraded in a natural manner<sup>[2]</sup>. Metals can be distinguished from other toxic pollutants, since they are non-biodegradable and can accumulate in living tissues, thus becoming concentrated throughout the food chain.

With the realization that water pollutants affect human and animal life in domestic and industrial activities, the pollution control and management is now a high priority area in world. Decontamination of heavy metal and its ion polluted soil and water by plants is called to phytoremediation. Phytoremediation is a plant-based approach to degrade organic pollutants in the soil and basically refers to the use of plants and associated soil microbes to reduce the concentrations or toxic effects of contaminants in the environment. Phytoremediation is widely accepted as an eco-friendly approach that could be a successful mitigation measure to revegetate heavy metal-polluted soil in a cost-effective environmental restoration technology<sup>[3]</sup>.

It has widely been reported that *Aloe vera* has been used for medical uses to their antimicrobial and anti-inflammatory epithelial-regenerative actions. In present review we focused on removal of heavy metals by use of aloe vera and its leave-waste powder; biosorption and bioleaching of heavy metals using *Bacillus licheniformis* strain in aloe vera gel. Furthermore *Aloe vera* using as one of phytoremediation is reviewed. Detoxification of heavy metals, and chronic kidney disease and uremic toxins, by aloe vera extract was discussed. In case reports the prevention of gall bladder hypertrophy and ureteral stone formation by aloe vera juice supplements was described.

## REMOVAL OF HEAVY METALS USING ALOE VERA AS AN ADSORBENT

Elimination of toxic heavy metals is attended by many researchers and there are various methods for the removal of heavy metals: chemical precipitation, reverse osmosis, ion exchange, coagulation, and adsorption. Succulent plant species, *Aloe vera* are investigated their ability to accumulate heavy metals and their uptake rate of different heavy metals by Elhag et al<sup>[1]</sup>. The study aimed to measure the concentration of toxic heavy metals (As, Cd, Cr, Pb, Hg and Ni) in dry-contaminated soils of Saudi Arabia. Aloe vera had the ability to decontaminate heavy metals from polluted soil. The greatest accumulation was detected from As<sup>3+</sup> but the accumulation was declined after 9 months. Hg<sup>2+</sup> accumulation showed no significant results of heavy metal uptake by *Aloe vera*. Recent adsorption techniques for wastewater treatment have become more popular with regard to their efficacy in the removal of pollutions, especially heavy metal ions. An adsorbent was developed from *Aloe vera* mature leaves for removing Pb<sup>2+</sup> from wastewater. Adsorption was carried out in a batch process with chemically modified *Aloe vera* which has prepared with the help of phosphoric acid (H<sub>3</sub>PO<sub>4</sub>). Chemical modification of *Aloe vera* with H<sub>3</sub>PO<sub>4</sub> increased in the sorption ability of *Aloe vera* for Pb<sup>2+</sup>. Malik et al<sup>[4]</sup> investigated the biosorption characteristics for Pb<sup>2+</sup> and examined the optimum conditions of the biosorption processes. Aloe vera plant was proved to be an excellent biomaterial for accumulating lead from aqueous solutions. The surface functional groups of adsorbent were examined

by FT-IR and contributed to the adsorption for Pb<sup>2+</sup>. The authors<sup>[5]</sup> developed a newly smart pouch with enclosed biomaterial (*Aloe vera* and coconut husk powder) for elimination of heavy metals from wastewater. A good correlation was found between experimental methods and theoretical findings. The major component of *Aloe vera*, aloe-emodin, has greater electron density of oxygen present on the planer conjugated anthraquinone ring system of aloe vera molecules. The hydroxyl atom ions are expected to contribute to the interaction with the heavy metals. *Aloe vera* contains aloin and aloe-emodin which may have a variety of chelation and antioxidant properties and include the protective role for heavy metal toxicity. Rai et al<sup>[6]</sup> assessed the accumulation of the essential elements require for the growth and heavy metals (Na, K, Ca, Mg, P, Cu, Zn, Cd, and Pb) in *Aloe vera* leaves growing in different geographical location of India. The results revealed that the composition of metals in *Aloe vera* is dependent on the chemical composition of soil and its direct use as cosmetic and for medicine is risky. The results showed that *Aloe vera* plant can be used as a good phytoremediation agent as it absorbs heavy metals from the soil in high quantity.

As *Aloe vera* can easily grow in Iran climates and due to vast probable contaminations from Iranian natural gas transmission pipelines industry (INGTPI), the main purposes of this study by Ziarati et al<sup>[7]</sup> investigated to decrease the risk levels for welders exposed to welding heavy metals in INGTPI and determine the potential ability of *Aloe vera* for cleaning up contaminated welding sites soil and the probable capability of this plant to extract different metals (Cr, Ni, Cu, Co, Pb and Cd) and also determine metal transfer factors from soil by *Aloe vera* in order to ascertain its phytoremediation potential. The results showed that *Aloe vera* transition factors for all heavy metals in treated soil were higher than one and *Aloe vera* can uptake Pb and Cu after 20 days more than other studied metals. The best result of Cd phyto-extract was in pH of soil 6.3 by 40 day growth of plants. The maximum Co, Cu and Ni uptake rate was in pH 6.1, 5.9 and 6.3, respectively by 40 day grown-*Aloe vera*.

The potential ability of *Aloe vera* for cleaning up contaminated educational sites of soil and the probable capability of this plant to phyto-extract different metals (Cr<sup>3+/6+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Pb<sup>2+</sup>, Cd<sup>2+</sup>) were studied by Shokri et al<sup>[8]</sup>. The phyto-mediation of Pb<sup>2+</sup> and Cd<sup>2+</sup> trend by this plant indicated that *Aloe vera* cultivated in the soil can be consider as a suitable hyper-accumulator by its relatively large ration of biomass concentration of the contaminant to soil concentration. The result showed that *Aloe vera* is effective and inexpensive adsorbent for the removal of Pb<sup>2+</sup>, Cd<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Cr<sup>3+/6+</sup> from contaminated soil by heavy metals.

The heavy metals released into the water bodies are Cu<sup>2+</sup>, Zn<sup>2+</sup>, Pb<sup>2+</sup>, Cr<sup>3+/6+</sup>, Cd<sup>2+</sup> etc., which were considered as toxic pollutants. Cu<sup>2+</sup> are water-soluble, where they function at low concentration as bacteriostatic substances, fungicides, and wood preservatives. In sufficient amounts, they are poisonous to higher organisms, at lower concentrations it is an essential trace nutrient to all higher plant and animal life. Excessive ingestion of copper brings about serious toxicological concerns, such as vomiting, cramps, convulsions, or even death. Sigh et al<sup>[9]</sup> investigated the removal of Cu<sup>2+</sup> from wastewater by *Aloe vera* using batch adsorption technique. *Aloe vera* for Cu<sup>2+</sup>-removal was investigated as a function of pH, dose, initial concentration, contact time and temperature. The kinetics, isotherms and thermodynamics were also studied for the batch study. *Aloe vera* has been used as an adsorbent for removal of copper from synthetic aqueous solution of copper sulfate by biosorption using batch process.

## BIOSORPTION OF HEAVY METALS BY ALOE VERA LEAVES WASTES POWDER

Batch adsorption of  $Cd^{2+}$  on *Aloe vera* leaves residue powder was determined by Gupta and Jain<sup>[10]</sup>. Adsorption behaviors were determined by varying operating parameters such as pH, initial concentration, doses, the temperature and contact time. At 0.6g bioadsorbent dose and the initial concentration of  $Cd^{2+}$  100mg/L, the equilibrium time and optimum pH value were found to 59.2% removal of  $Cd^{2+}$ . The research on aloe vera use which is related to environmental application such as clean water technology/wastewater treatment process has been focused on using aloe vera waste biomass-based sorbents for the removal of heavy metals, dyes and other pollutants from aqueous media. The biosorption of  $U^{6+}$  and  $Cd^{2+}$  using aloe vera wastes was investigated by Noli *et al*<sup>[11]</sup> regarding the effect of pH, sorbent mass, concentration, contact time and temperature. It was found that the biosorbent modified by alkaline reagent, exhibited high sorption capability with  $q_{max}$  values, 370.4 and 104.2 mg/g for  $U^{6+}$  and  $Cd^{2+}$ , respectively. *Aloe vera* is proposed as potential biosorbent for  $U^{6+}$  and  $Cd^{2+}$  in acidic solution. The biosorption potential of  $Na_2CO_3$ -modified *Aloe barbadensis* leaf powder (MABL) for removal of  $Ni^{2+}$  from a synthetic aqueous solution was investigated by Gupta and Kumar<sup>[12]</sup>. Effects of various process parameters (pH, equilibrium time, and temperature) were investigated in order to optimize the biosorptive removal. The maximum biosorption capacity of MABL was observed to be 28.986 mg/g at a temperature of 303K, a biosorbent dose of 0.6g, a contact time of 90 min, and a pH value of 7.0. Biosorption studies in batch mode were carried out by Gupta and Kumar<sup>[13]</sup> to investigate the adsorption of  $Ni^{2+}$  from aqueous solution on *Aloe vera* leaves residue powder. The maximum biosorption of 60.2% for an initial  $Ni^{2+}$  concentration of 100 ppm was achieved. The results showed that aloe vera leaves residue has the potential to be used as a low-cost biosorbent for the removal of  $Ni^{2+}$  from wastewater.

## CHARACTERIZATION OF BACILLUS LICHENIFORMIS STRAIN FOR BIOLEACHING OF HEAVY METALS

Although conventional techniques are well known for heavy metals removal from the environment, their high cost and severe environmental consequences are required. As the urgent requirement of cost-effective-rapid methods with biological assessment of heavy metals uptake, bioaccumulation can be considered as an alternative method. Bioleaching is a process of extracting metals from waste by using microorganisms to oxidize the metals, producing soluble compounds, so that the elements can be extracted from a material when water is filtered through it. Abraham *et al*<sup>[14]</sup> investigated the isolation of heavy metals tolerant Gram-positive bacteria strain: *Bacillus licheniformis* JAJ3, and its application in bioaccumulation of  $Cu^{2+}$ ,  $Pb^{2+}$ , and  $Ni^{2+}$  and bioleaching of heavy metals from electronic waste. The organism was able to accumulate 98.6%  $Cu^{2+}$ , 64.6%  $Pb^{2+}$ , and 57.3%  $Ni^{2+}$ . The experimental analyses confirmed that the strain is efficient in the bioleaching of heavy metals from electronic wastes and thus can be used in management of the electronic wastes.

As the endophytic microbiota of *Aloe vera* gel, the following microbiomes were identified in previous paper: *Bacillus cereus*, *B. licheniformis*, *Lactobacillus paralimentarium*<sup>[15]</sup>. *Aloe vera* leave therefore could be used as bioleaching of heavy metals.

## DETOXIFICATION OF HEAVY METALS BY ALOE VERA

The global heavy metal pollution of water is a major environmental problem with the advent of agricultural and industrial revolution, in which most of the water resources are becoming contaminated. Industrial discharges containing toxic and hazardous substances, including heavy metals contribute tremendously to the pollution of aquatic ecosystem causing cytotoxic, mutagenic and carcinogenic effects in fish and animals. Fish are at the top of aquatic food chain and may concentrate large amounts of metals from the water. Zoda<sup>[16]</sup> investigated the effect of aloe vera juice on toxicity induced by chromium on *Labeo rohita* fingerlings, exposed to sub-lethal concentration of chromium and aloe vera juice for 21 days. In both the liver and muscle tissues a pronounced effect of chromium and aloe vera juice was noted on activities; GOT, GPT, ACP, and ALP, etc. The results suggested that aloe vera juice has an effective hepato-protective and tissue protective property against chromium toxicity. Siu *et al*<sup>[17]</sup> investigated the study based on a hypothesis that aloe vera extracts could have lead binding effects and could be developed as a food supplement, aloe vera extracts to prevent accumulative lead. Lead contents in blood and tissues in Sprague-Dawley male rats were highest in the intra-peritoneal injection: while *Aloe vera* and pectin were used separately or in combination to counteract the 6 weeks continuous ingestion of lead, the changes in the blood, liver, kidney and bone were not impressive. While *Aloe vera* and pectin were used separately or in combination to counteract the shorter 2 weeks continuous ingestion of lead, high dose of *Aloe vera* gave a trend of decline in the lead content of blood. *Aloe vera* and/or pectin showed a trend of lowering the lead contents in liver, kidney but not bone when high doses were given. The preliminary study supports the hypothesis that *Aloe vera* could be used as a safe supplement to prevent the accumulation of ingested lead.

## DETOXIFICATION OF ALUMINUM BY ALOE VERA

Aluminum enters the human body via food, air, water and drugs, and is present in many manufactured foods such as processed cheese, etc., and pharmaceutical products, especially antacids. Jakkala and Ali<sup>[18]</sup> investigated the protective role of *Aloe vera* extract on  $Al^{3+}$  induced neuro-degenerative changes in brain of albino rats. While examination of brain sections,  $Al^{3+}$  treated group *per se* showed abnormal characteristic architecture compared with the control group. Rat exposed to pre-calculated dose of aluminum sulfate for 30 days did not show any notable alterations in brain histology, whereas rats exposed to the same dose for 60 days intoxication showed significant neurodegenerative changes in the hippocampus, amygdala, motor cortex, and cerebellum. It was also observed that supplementation of aloe vera extract noticeably reduced degenerative changes caused by  $Al^{3+}$  and improved the architectural histology of brain and significantly reduced brain damage and improved functional outcome. Mahor *et al*<sup>[19]</sup> investigated the nephron-protective effect of *Aloe vera* and aloe in aluminum sulfate exposed rats for a period of 45, 90, and 180 days. Several creatinine, urea and uric acid levels were found to significantly increased after treatment of  $Al_2(SO_4)_3$  in group II compared to control group I animals fed with normal diet. Co-treatment with  $Al_2(SO_4)_3$  and *Aloe vera* extract (group III) and aloe (group IV) showed significant decrease in creatinine, urea and uric acid. The study demonstrated that *Aloe vera* (group III) and aloe (group IV) were effective in reducing aluminum toxicity

in kidney. *Aloe vera* and aloin can be used as adjuvant therapy for the prevention and management of aluminum sulfate induced renal damage.

#### Recent research on the relation of aluminum; dementia and Alzheimer's disease

Naturally-occurring metals such as copper and iron are present in our bodies. Small amounts of these metals are essential to keeping our brains and bodies working properly. Most aluminum taken into the body is cleaned out by the kidney. Recent study finds a potential role for high dose aluminum in drinking water in progressing Alzheimer's disease (AD) for people who already have the disease. Aluminum accumulation has been associated with AD for nearly half a century. Tau and Amyloid- $\beta$  are known to act in synergy to produce neurotoxicity in AD and a role of aluminum in this process was presented by Mold and Exley<sup>[20]</sup>.

### THE PROTECTIVE EFFECT OF ALOE VERA GEL POWDER AGAINST SO<sub>2</sub> GAS

Air pollution has become a serious environmental issue and a threat to all over the world and SO<sub>2</sub> is the most poisonous and irritant gas as it penetrates deeply in vitals; heart and lungs. Yadav<sup>[21]</sup> investigated the protective effect of *Aloe vera* gel powder against SO<sub>2</sub> induced hepatotoxicity in albino rats. SO<sub>2</sub> caused significant increase in total bilirubin, conjugated bilirubin, serum enzymes AST, ALT, GGT, and ALP in liver of albino rats. Oral administration of *Aloe vera* gel powder recovered all these alterations at their normal level which is an indication of remedial effect of *Aloe vera* gel powder on SO<sub>2</sub> induced hepatotoxicity.

### EFFECT OF HEPATO-THERAPEUTIC EFFECT OF ALOE VERA GEL

#### The influence of long-term Aloe vera ingestion on age-related disease in male Fisher 344 rats

Ikeno et al<sup>[22]</sup> investigated the effects of long-term aloe vera ingestion on age-related diseases using male specific pathogen-free Fisher 344 rats. The results showed life-long aloe vera ingestion does not cause any of obvious harmful and deleterious side effects, and could be beneficial for the prevention of age-related pathology.

#### Efficacy of dietary aloe vera supplementation on hepatic cholesterol and oxidative stress in aged rats

Using male specific pathogen-free Fisher 344 rats, Lim et al<sup>[23]</sup> studied that a life-long intake of aloe vera ingestion had superior anti-oxidative action against lipid peroxidation in vivo, as indicated by reduce levels of hepatic phosphatidylcholine hydroperoxide. Additionally anti-oxidative action was evidenced by enhanced SOD and catalase activity. Furthermore, the study revealed that hepatic cholesterol significantly increased in the control group during aging in contrast to the aloe-supplement groups, which showed approximately 30% lower cholesterol levels, thereby an effective hypocholesteremic efficacy. The authors suggest that life-long dietary aloe supplementation suppresses free radical-induced oxidative damage and age-related increase in hepatic cholesterol.

#### Hepatotherapeutic effect of aloe vera gel in alcohol-induced hepatic damage

Saka et al<sup>[24]</sup> evaluated the hepatotherapeutic activity of aqueous extract of aloe vera gel in rats.

Hepatotoxicity was induced in the positive control and extract-treated rats with alcohol. The hepatotherapeutic effect was evaluated by performing an assay of serum total bilirubin, etc., and liver histopathology. Aloe vera gel treatment maintained hepatic architecture similar to that seen in the control. The results lent credence to the use of *Aloe vera* in the management of alcohol-induced hepatic dysfunction. Furthermore the authors investigated changes in serum electrolytes urea and creatinine in aloe vera-treated rats, and concluded that aloe vera extract impairs renal handling of electrolytes with consequent hyponatremia and hypercreatinemia<sup>[25]</sup>.

#### Effects of aloe vera gel extract on liver and kidney function changes in H<sub>2</sub>O<sub>2</sub>-induced rats

Abdal et al<sup>[26]</sup> investigated the role of aloe vera gel extracts on lipid profiles and liver and kidney functions in rat drinking water that containing 1% hydrogen peroxide in a dark bottle for 21 days. The results showed that aloe vera gel extract is effective to improve the lipid profile (by lowering LDL, TG, and increasing HDL) and liver and kidney function (by reducing concentration of ALT and AST).

#### Protective effect of aloe vera extract on liver diseases of experimental rats

Ismael et al<sup>[27]</sup> evaluated the hepatoprotective effects of aloe vera against hepatotoxin-induced liver damage. *Aloe vera* improved liver and kidney histopathology in carbon-tetrachloride-induced hepatotoxicity in rats fed on different ratios of its extract.

### EFFECT OF ALOE VERA GEL EXTRACT ON ANTIOXIDANT ENZYMES AND AZOXYMETHANE-INDUCED OXIDATIVE STRESSES IN RATS

Azoxymethane (AOM) is reported to generate the extremely reactive hydroxyl radical inducing oxidative stress that participates in peroxidation of the membrane lipids leading to the increased malon-dialdehyde formation. AOM metabolized in liver to methyl azoxymethanol leads to methyl carbonium ion. Methyl carbonium ion: CH<sub>3</sub><sup>+</sup> is believed to be the ultimate carcinogen which binds stem cells DNA in colon. Anilakumar et al<sup>[28]</sup> investigated the effect of oral feeding of 2% aloe vera gel extract (AGE) for 30 days on AOM-induced oxidative stress in rats. Ingestion of AGE effected reduction in AOM-induced colonic GSH-peroxidase, G-6-PD and glutathione S-transferase, and femur bone marrow micronuclei formation. The results strongly suggest that AGE possesses the ability to reduce AOM-induced oxidative stresses and toxicity in liver.

### ANTI-OXIDATIVE AND ANTI-FIBROTIC EFFECTS OF ALOE VERA HYALURONAN IN PATIENTS WITH LIVER FIBROSIS

Oxidative stress has been recognized as a fundamental factor in the pathological changes observed in various liver diseases. It can cause excessively harmful damage to hepatocytes through lipid peroxidation and protein alkylation<sup>[29]</sup>. Aloe vera extracts have been used for medical uses to their antimicrobial, anti-inflammatory epithelial-regeneration actions. Extraction of hyaluronic acid (HA) from just below the rind part, there is an area where aloe correlated bacteria; *Streptococci* live, of *Aloe vera* was reported by Putri<sup>[30]</sup>. The authors found out that the rind part of aloe vera have the highest

potential of high content of HA. HA is studied as a non-invasive marker of liver fibrosis in chronic liver diseases, in an attempt to avoid the complications of liver puncture biopsy, considered the gold standard in the evaluation of fibrosis. Orasan *et al*<sup>[31]</sup> reviewed the advantages and limitations of HA, a biomarker, used to manage patients with chronic viral hepatitis B or C infection, non-alcoholic fatty liver disease, HIV-HCV coinfection, alcoholic liver disease, primary biliary cirrhosis, biliary atresia, hereditary hemochromatosis and cystic fibrosis. HA has been shown to promote angiogenesis. HA is a widely used natural material for cell transplantation due to its biocompatible and tunable nature. For the liver, HA is the main component of the perisinusoidal space and combined with its high hydrophilicity to form a hydrogel<sup>[32]</sup>.

Currently, acute and chronic liver diseases pose a global concern and treatment for these diseases is difficult and has limited efficacy. Viral hepatitis is the most common cause of acute and chronic liver disease in the world and the over half of the world's population are exposed to the different kind of hepatotropic viruses. Our early study investigated the anti-oxidative and anti-fibrotic effect of aloe vera in patients with liver fibrosis and suggested that the oral supplementation with aloe vera high molecular fraction could be helpful in alleviating the fibrosis and inflammation of hepatic fibrosis patients<sup>[33]</sup>. The epigenetic roles of the gut microbiome in aloe vera ingestion may play an important role for the prevention to COVID-19 and the targeting gut dysbiosis could help control the pathogenesis of COVID-19<sup>[34]</sup>.

The prospective, randomized, open, parallel group, interventional study was carried out by Bhatt *et al*<sup>[35]</sup> in a tertiary care hospital which was designed to evaluate the hepato-protective activity of aloe vera juice (AVJ), orally ingested 20 ml, twice daily. Fifty patients belonging to control group received conventional treatment for acute viral hepatitis, while 60 patients enrolled in treatment group were given conventional treatment for acute viral hepatitis supplemented with AVJ, orally in dose of 20 ml, twice daily. Intragroup comparison using repeated measure ANOVA demonstrated a statistically significant decrease in parameters; serum bilirubin, serum ALT, serum AST and serum ALP levels for both treated and control groups at all intervals of time. Intragroup comparison done by student-t-test revealed statistically significant difference in all the mentioned parameters between treated and control groups at all intervals of times. The study evaluated the hepatoprotective activity of AVJ in patients with acute liver disease.

## THE CHELATION OF $Fe^{3+}$ TO HYALURONAN (HA) AND THE MAGNETIC SYNTHESIS OF HA AS ADSORBENT FOR $Cu^{2+}$

Regulation of the activity of matrix metalloproteinase (MMPs) is a potential strategy for osteoarthritis (OA) therapy. Gao *et al*<sup>[36]</sup> reported an injectable and self-healing hydrogel enabling factor-free MMP regulation and biomechanical competence in situ. Addition of a  $Fe^{3+}$ -GSH complex to an aqueous solution of HA led to full gelation and Fe-coordination provided the self-healing HA gel with chondrocyte tolerance. The gel demonstrated higher MMP-13 regulation than a commercial HA joint injection and the successfully inhibited synovial fluid MMPs of an osteoarthritic patient. Fe-coordination to HA in aqueous environment generates an injectable self-healing and biomechanically viable gel and enables factor-free regulation of matrix MMPs. These results open up new possibility in the use of HA as both mechanically-competent hydrogel as well as a mediator of MMP regulation for OA therapy. Magnetic HA microspheres were

fabricated as a novel adsorbent through the immobilization of HA on the magnetic silica microspheres. HA was utilized as adsorbent for the heavy metal removal. The resultant microspheres revealed super-paramagnetic behavior, which made these adsorbent magnetically separable after the adsorption performance. Lan *et al*<sup>[37]</sup> demonstrated that the synthesized HA-supported magnetic adsorbent can be considered as a potential adsorbent for hazardous metal ions from wastewater.

## DETOXIFICATION OF ALOE VERA GEL FOR OXIDATIVE LIVER STRESS

### Protection of oxidative liver damage

Nahar *et al*<sup>[38]</sup> investigated the hepato-protective potential of aloe vera gel as a dietary supplement, designed in vitro and in vivo experimental models of chemical-induced liver damage by use of male Sprague-Dawley rat. Dietary aloe vera gel showed significant hepato-protection against  $CCl_4$ -induced as evident by restoration of liver lipid peroxide serum, serum transaminase, alkaline phosphatase, and total bilirubin towards near normal.

### Detoxification effects of aloe polysaccharide and propolis on urinary excretion of metabolites in smokers

The effects of aloe polysaccharide (APS), propolis, and the mixture on urinary excretion of tobacco smoking carcinogens, benzo[a]pyrene (BaP) and nicotine were investigated by Koo *et al*<sup>[39]</sup>. The urinary excretion of BaP and cotinine (a metabolite of nicotine) was significantly enhanced by supplementation of APS, propolis, and the mixture. APS and propolis supplements might protect smokers from tobacco-related diseases by compensating creatinine, glucose, and total bilirubin.

## EFFECTS OF ALOE VERA PREVENTING KIDNEY STONE FORMATION AMONG ADULTS

Kirdpon *et al*<sup>[40]</sup> investigated the amount of citrate and tartrate in aloe vera gel, and in the urine of healthy normal thirty one volunteers, before and after consuming fresh aloe gel, and determined the value of consuming aloe gel for prevention of renal stone formation. The results showed that calcium salts were made more soluble in the urine. The tendency for an increase in the permissible increment (PI) in oxalate, albeit statistically non-significant, indicates that oxalate salts in the urine are possibly inhibited from precipitation. According to the low oxalate excretion in the urine and increasing PI in calcium, the authors concluded that aloe composition has a beneficial effect for the prevention of both calcium and oxalate stone formation in adults.

## BENEFICIAL ROLES OF ALOE VERA FERMENTED BUTYRATE, PROPIONATE, AND ALOIN TO CHRONIC KIDNEY DISEASE, UREMIC TOXINS AND VIRAL INFECTIONS

Chronic kidney disease (CKD) is a global health problem that brings to a substantial risk for end-stage renal disease, cardiovascular disease, and death. In CKD, the accumulation of gut-microbial derived uremic toxins, such as indoxyl- and p-cresol sulfate accelerates the progression of CKD and mortality. Gut microbiota has been recognized as an important endogenous organ. The kidney-gut axis would contribute to gut dysbiosis which might worsen CKD.

The interest in butyrate producing endophytic bacteria in *Aloe vera* to CKD and uremic toxins was reported<sup>[41]</sup>.

In case reports for medical treatment of steroid-sensitive nephrotic kidney syndrome in children, beneficial roles of successive ingestion of aloe vera juice (AVJ) was reported in the previous paper<sup>[42]</sup>. Furthermore in the case reports of prophylactic role of aloe components, it was reported that successive ingestion of aloe vera juice may decrease the risk for the steroid-induced osteonecrosis of femoral head after kidney nephrosis. The successive ingestion of aloe vera juice suggests that aloe vera fermented butyrate may blunt osteoclastogenesis and bone resorption, and stimulate bone formation<sup>[43]</sup>. In previous case reports we showed beneficial roles of Kampo medicine with AVJ to influenza virus and norovirus<sup>[44]</sup>.

## PREVENTION OF ACUTE RADIATION-INDUCED PROCTITIS BY ALOE VERA

Acute radiation-induced proctitis (ARP) is the most common side effect following radiotherapy for malignant pelvic disease. Sahebnaasagh *et al*<sup>[45]</sup> evaluated the efficacy of aloe vera gel ointment in prevention of ARP. Forty-two patients receiving external-beam radiotherapy (RT) for pelvic malignancies were randomized to receive either aloe vera 3% or placebo topical ointment during radiotherapy for 6 weeks. The results showed that aloe vera gel topical ointment was effective in prevention of symptoms of ARP in patients undergoing RT for pelvic cancers. Trial registration: IRCT201606042027N6.

## CASE REPORT: PREVENTION OF GALL BLADDER HYPERTROPHY AND URETERAL STONE BY ALOE VERA JUICE SUPPLEMENTS

**Case report 1:** A ~60 years-female frequently had abdominal bloating and strong vomiting in Jan, 2015. She started to drink Sake after having the troubles in her family in Jan, 2017. Then she had severe stomach ache and was diagnosed gall bladder hypertrophy with gallstone ache on Feb. 21, 2017. The blood examination showed bilirubin level at 6.0 mg/dL and white blood cells number at 18,000/ $\mu$ L. She was recommended surgery, but she refuses the surgery. After she took aloe vera juice (AVJ, 600ml/day) with supplements (bee pollen and bee propolis) for one month, the blood examination showed bilirubin level at 1.0 mg/dL and white blood cells number at 6,000/ $\mu$ L. The gallstone showed smaller than that before on Feb. 21, 2017. Since then she takes care of the dietary with ingestion of AVJ (600ml/day) and is well recovered without drink Sake and no trouble of gallstone formation in 2021.

**Case report 2:** A ~32 years-female having allergic constitution took care of the diet with calcium supplements. On eight months pregnant she had severe stomachache and was diagnosed ureteral stone. The doctor recommended not take medicine because of her pregnancy, but recommended her to drink a lot of water. Then she started to drink aloe vera juice (2000 ml/day) for one week. She excreted stone with urea and the doctor determined it calcium stone. After safe delivery she takes AVJ (200 ml/day) for 20 years to May, 2021 and has no recurrence of the illness and was well-being QOL.

### Case report discussion

Investigation of detoxification effects showed the restoration of urinary functions by aloe vera juice (AVJ) supplements. Fresh aloe vera gel (100g) contains 96.3mg of citrate and 158.9mg of tartrate. Changes in chemical compositions of urine after the ingestion of

AVJ containing citrate and tartrate show its potential for preventing kidney stone formation among adults. The urinary excretion of oxalate was significantly decreased<sup>[40]</sup>. Case reports provided a new beneficial evidence of AVJ supplements for gall bladder hypertrophy and ureteral stone.

## SUMMARY

*Aloe vera* has the ability of phytoremediation to remove heavy metals from contaminated soil polluted with metals such as  $As^{3+}$ ,  $Cd^{2+}$ ,  $Cr^{3+/6+}$ ,  $Cu^{2+}$ ,  $Pb^{2+}$ ,  $Hg^{2+}$ , and  $Ni^{3+}$ , due to the great reduction of these metals in contaminated soils. The characterization of *Bacillus licheniformis* strains which are identified as the endophytic microbiota of *Aloe vera* gel indicated the possible application for bioleaching of heavy metals. Furthermore detoxification of heavy metals and aluminum, and hepato-therapeutic and anti-oxidative, anti-hepatic, anti-fibrotic effects, and anti-osteoclastogenesis of *Aloe vera* was discussed. The potential use of *Aloe vera* may provide fresh insights to phytoremediation processes for heavy metals, polluted soil and  $SO_2$  gas. Anti-oxidative and anti-fibrotic effects of aloe vera hyaluronan were described. Case reports exhibited that the dietary aloe vera juice supplementations could support the improvement of QOL in gall bladder hypertrophy and the suppression of ureteral stone formation.

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