A Review On The Potential Of Spirulina And Its Application In Nutraceuticals And Pharmaceuticals

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ABSTRACT

Microalgae and lactic acid bacteria have become an innovative and promising resource of nutritional supplements as they are commercially cultivated to produce valuable compounds, including protein, pigments, lipids, essential amino acids, monounsaturated and polyunsaturated fatty acids, carotenoids, steroids and vitamins. The pharmacological actions, such as nutraceutical improvements, lowering LDL cholesterol levels, anti-inflammation, antioxidation, antitumor, immunological enhancement, and hepatorenal protection from *Spirulina* spp and Lactic acid Bacillus have been reported recently. Based on the therapeutic potential of spriulina fermentation based lactic acid bacteria, different application studies such as, determining the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on enhancing the Nutraceutical properties of *Spirulina* species, investigating the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on lowering HDL cholesterol, and evaluating the cytotoxic effect and influence of FSL on human cancer cell line was reviewed in the current article.

Key words: Spirulina fermentation, Lactic acid bacteria, cholesterol, anti-cancer

INTRODUCTION

Along with the development of marine biological pharmaceutical research, higheffective and low-toxic drugs and functional foods isolated from marine organisms have become a new field of pharmacy and bromatology. The pharmacological actions, such as nutraceutical improvements, lowering LDL cholesterol levels, anti-inflammation, antioxidation, antitumor, immunological enhancement, and hepatorenal protection of Cphycocyanin (C-PC) from Spirulina platensis, and bacteriocin from probiotic lactic acid bacillus have been reported. C-PC has important value of development and utilization either as drug or as functional food. Lactic acid bacteria (LAB) are beneficial probiotic organisms that contribute to improved nutrition, microbial balance, and immuno-enhancement of the intestinal tract, as well as lower cholesterol. There are many researches about the various pharmacological actions and mechanisms of C-PC, but related reports are only to some extent integrated deeply and accurately enough, which put some limitations to the further application of C-PC in medicine. Particularly, with the improvement of living standards and attention to health issues, C-PC being a functional food is preferred by more and more people. C-PC is easy to get, safe, and nontoxic; thus, it has a great potential of research and development as a drug or functional food. Here, the separation and purification, physicochemical properties, physiological and pharmacological activities, safety, and some applications are reviewed to provide relevant basis for the development of natural medicine and applied products. Over the last few decades, products from natural, non-synthetic origin have become increasingly important for the prevention and treatment of cancer due to the toxic side effects of many synthetic anti-cancer drugs. Arthrospira platensis (AP), often called "Spirulina", belongs to the phylum of cyanobacteria with characteristic photosynthetic capability. These filamentous, gram-negative cyanobacteria or blue-green algae are considered as one of the sources of such natural bioactive substances (Qian Liu et al., 2016).

Based on the therapeutic potential of spriulina fermentation based lactic acid bacteria, different application studies were reviewed in the present article. The applications are as follows,

- determining the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on enhancing the Nutraceutical properties of *Spirulina* species,
- investigating the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on lowering the LDL cholesterol and increasing HDL cholesterol, and

> evaluating the cytotoxic effect and influence of FSL on human cancer cell line.

Many researchers were worked on each of these above applications. The literature survey on these individual application works were collected and reviewed in this article for better understanding.

1. Determining the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on enhancing the Nutraceutical properties of *Spirulina* species

The effect of fermentation using Spirulina culture with lactobacillus species for increasing the nutraceutical potential was studied by Elena de Marco Castro et al.,(2019). The researchers used a filamentous fresh-water planktonic cyanobacterium called Arthrospira *platensis*. It has been reported to contain diverse biological activities and a unique nutritional profile, due to its high content of valuable nutrients. This study aimed to further improve the bioactive profile of Spirulina, by fermenting it with the lactic acid bacterium Lactobacillus plantarum. In vitro comparison of the total phenolic content (TPC), C-phycocyanin, free methionine, DPPH radical scavenging capacity, ferric reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC) and protein fragmentation via SDS-PAGE in untreated versus 12 to 72 h fermented Spirulina is reported here. After 36 h fermentation, TPC was enhanced by 112%, FRAP by 85% and ORAC by 36%. After 24 h, the DPPH radical scavenging capacity increased 60%, while the free methionine content increased by 94%, after 72 h. Past 36 h of fermentation, the total antioxidant capacity (TAC) diminished, possibly due to deterioration of the heat-sensitive antioxidants. However, protein fragmentation and free methionine content increased, linearly, with the fermentation time. Cyanobacterial peptides and other bioactive compounds trapped within the Spirulina cell wall are released during fermentation and have a significant potential as a functional ingredient in nutraceuticals and pharmaceuticals, in addition to their nutritive value.

Recently, Alberto Niccolai (2020) evaluated the suitability of *Arthrospira platensis* F&M-C256 (*Spirulina*) biomass in a vegetal soybean drink or in water, as substrate for lactic acid fermentation by the probiotic bacterium *Lactiplantibacillus plantarum* ATCC 8014 (LAB8014) and to evaluate the fermented products in terms of bacteria content and organic acids content, biochemical composition, total phenolics, and phycocyanin content, *in vitro* digestibility, *in vitro* and *in vivo* antioxidant activity. After 72 h of fermentation, a bacterial concentration of about 10.5 log CFU mL⁻¹ in the broths containing the soybean drink + *Spirulina* + LAB8014 (SD + S + LAB8014) or water + *Spirulina* + LAB8014 (W + S

+ LAB8014) was found. Lactic acid concentration reached similar values (about 1.7 g L⁻¹) in the two broths, while a different acetic acid concentration between SD + S + LAB8014 and W + S + LAB8014 broths was observed (7.7 and 4.1 g L⁻¹, respectively). *A. platensis* biomass was shown to be a suitable substrate for LAB8014 growth. After fermentation, both broths contained a high protein content (>50%). In both broths, total phenolics, *in vitro* and *in vivo* antioxidant activity increased after fermentation (+35, +20, and +93% on average, respectively), while phycocyanin content decreased (-40% on average). Digestibility of W + S + LAB8014 broth statistically improved after fermentation. This study highlights the potential of *A. platensis* F&M-C256 biomass as a substrate for the production of new functional lactose-free beverages.

In another nutraceutical studies conducted by Antonia Terpou et al., (2020) produced a novel functional Feta-type cheese with incorporated Spirulina platensis and studied its effect on microflora and physicochemical properties of produced cheeses. Feta cheese was prepared with pasteurized sheep milk. The effects of supplemented S. platensis (0.25%) was studied during manufacture and storage (4 °C) of Feta-type cheese for 60 days and compared with commercial Feta cheese. Growth and viability of Lactobacilli and Lactococci was reported higher in cheese samples containing Spirulina as a result the starter culture (lactic acid bacterial culture) used in Feta cheese production is not disturbed can be even enhanced by the presence of microalgae. Specifically, S. platensis showed a positive effect on the growth of lactobacilli while lactococci viability was detected enhanced in cheese sample with incorporated Spirulina. In addition, no pathogenic microorganisms were detected after the 30th day of production. Finally, incorporation of Spirulina significantly affected the color and mouthfeel of produced cheeses while moisture was detected higher as the content of Spirulina increased. To conclude, Spirulina platensis has great industrialization potential as an additive in dairy products and especially ones produced by Lactobacilli as starter cultures while enhancing products nutritional value in parallel.

In a very recent study, Sylwia Scieszka et al., (2021) produced a lactose-free product with *Chlorella vulgaris*, by using a large amount of lactic acid bacteria (LAB). The survival rate of *Levilactobacillus brevis* in soya drink with *Chlorella vulgaris* during 30 days of storage at 4 °C was higher than in soya drinks without algae. Moreover, *Chlorella vulgaris* caused an increase in L-lactic acid production by LAB in the soya drinks. From the high concentration of bacterial cells (8.49 log CFU/mL) in the fermented soya drink with

algae after 30 days of storage at 4 °C, the researchers can conclude that this microalga is a promising substrate for the production of fermented beverages. Furthermore, the soya drink with the *Chlorella vulgaris* and xylitol, due to the number of bacteria, also meets the criteria for a fermented probiotic product. The bacteria introduced into the gastrointestinal tract simulator together with a soya drink after the storage period exhibited a considerably higher survival rate, thus this indicating that the matrix provided protective conditions for them. The combination of *Chlorella vulgaris* and LAB in a soya drink provides the opportunity to create a functional plant-based product and opens new horizons for the food industry.

Beheshtipour et al., (2013) signifies the viability of probiotic lactic acid bacteria during the production and storage of fermented milks in the dairy industry. Addition of microalgae into milk for the production of fermented milk in order to enhance the viability of probiotics has been the subject of recent research. *Spirulina* and *Chlorella* are the most widely noted microalgae for fermented milks. They affect not only the viability of probiotics in final product but also the sensory attributes of them. Incorporation of microalgae into probiotic fermented milks along with enhancing the viability of probiotics would increase their functional characteristic. This is because they contain a wide range of nutrients and nutraceuticals and are considered as "functional food." This article reviews the effects of supplementation of *Spirulina platensis* and *Chlorella vulgaris* into probiotic fermented milks on their different quality characteristics.

Labuzer Celekli et al., (2018) fermented milk industry comprehensive probiotic bacteria are a popular and universal issue with trade significance. There are various products are obtainable in public markets. The viability of probiotic bacteria in final product of fermented milk and yogurt products up to the time of utilization is the most important object of search in milk industry. *Spirulina* is the most vastly famous microalgae utilized for enriching fermented milk products. That incorporation of *Spirulina* into probiotic fermented products along with promoting viability of probiotic bacteria will grow their functional properties due to their critical nutrient quality which is beheld as "functional food". Addition of microalgae especially *Spirulina* into fermented milk for promoting viability of probiotics and impacts on their acidification characteristics is a topic of this discussion.

Varga et al., (2002) investigated the effect of a cyanobacterial (*Spirulina platensis*) biomass on the microflora of a probiotic fermented dairy product during storage at two temperatures. *Spirulina*-enriched and control (plain) fermented acidophilus bifidus-

thermophilus (ABT) milks were produced using a fast fermentation starter culture (ABT-4) as the source of Lactobacillus acidophilus (A), bifidobacteria (B), and *Streptococcus thermophilus* (T). Incubation took 6 h at 40°C. As for the cyanobacterial product, the S. platensis biomass was added to the process milk during stirring at pH 4.5 to 4.6. Thereafter, the ABT type fermented milks were cooled to 25°C in ice water, filled into sterile, tightly capped centrifuge tubes, further cooled at 4°C for 24 h, and then stored either at 15°C for 18 d or at 4°C for 42 d. Microbiological analyses and acidity measurements were performed at regular intervals. Our results showed that the counts of the starter organisms were satisfactory during the entire storage period at both temperatures applied in this research. The *S. platensis* biomass had a beneficial effect on the survival of ABT starter bacteria regardless of storage temperature. Post acidification was observed at 15°C, whereas pH remained stable during refrigerated storage at 4°C. The abundance of bioactive substances in *S. platensis* is of great importance from a nutritional point of view because thus the cyanobacterial biomass provides a new opportunity for the manufacture of functional dairy foods.

2. Investigating the effect of *Spirulina* fermentation with Lactic acid bacteria (FSL) on lowering the LDL cholesterol and increasing HDL cholesterol

The effect of *Spirulina* and Lactic acid bacteria (FSL) on reducing the LDL cholesterol and/or enhancing the HDL level is investigated separately using animal models. Luciane Maria et al., (2008), used rabbits to experiment the efficiency of Spirulina in reducing LDL levels. In this work, hypercholesterolemia was induced in rabbits by feeding them a high cholesterol diet (CD, 350 mg/d) and the effects of supplementing this diet with 0.5 g/d *Spirulina* platensis was evaluated by measuring the levels of serum total-cholesterol (TC), triacylglycerols (TAG) and high-density lipoprotein (HDL-cholesterol) at the start of the experiment and after 30 d and 60 d. It was found that the levels of serum cholesterol decreased from 1,054 \pm 101 mg.dL-1 in the rabbits fed a CD without S. platensis (significant at p <0.0001). The addition of *Spirulina* to the cholesterolemic diet did not cause significative decrease on the levels of triacylglycerols in the animals. The levels of serum high-density lipoprotein (HDL-cholesterol) was 73 \pm 31 mg.dL-1 for rabbits fed a CD without S. platensis as compared to 91.0 \pm 15.7 mg.dL-1 in those fed a CD supplemented with S. platensis (significant at p=0.1533).

Cheng-Chih Tsai et al., (2014) collected different probiotic isolates from animal and plant sources to evaluate the bile-salt hydrolase activity of probiotics in vitro. The deconjugation potential of bile acid was determined using high-performance liquid chromatography. HepG2 cells were cultured with probiotic strains with high BSH activity. The triglyceride (TG) and apolipoprotein B (apo B) secretion by HepG2 cells were evaluated. Our results show that the BSH activity and bile-acid deconjugation abilities of Pediococcus acidilactici NBHK002, Bifidobacterium adolescentis NBHK006, Lactobacillus rhamnosus NBHK007, and Lactobacillus acidophilus NBHK008 were higher than those of the other probiotic strains. The cholesterol concentration in cholesterol micelles was reduced within 24 h. NBHK007 reduced the TG secretion by 100% after 48 h of incubation. NBHK002, NBHK006, and NBHK007 could reduce apo B secretion by 33%, 38%, and 39%, respectively, after 24 h of incubation. The product PROBIO S-23 produced a greater decrease in the total concentration of cholesterol, low-density lipoprotein, TG, and thiobarbituric acid reactive substance in the serum or livers of hamsters with hypercholesterolemia compared with that of hamsters fed with a high-fat and high-cholesterol diet. These results show that the three probiotic strains of lactic acid bacteria are better candidates for reducing the risk of cardiovascular disease.

Sun Hee Cheong et al., (2010) investigated the anti-atherogenic effects of *Spirulina* (*Spirulina* platensis) in the New Zealand White (NZW) rabbit model. The animal had hypercholesterolemia induced by being fed a high cholesterol diet (HCD) containing 0.5% cholesterol for 4 wk, and then fed a HCD supplemented with 1 or 5% *Spirulina* (SP1 or SP5) for an additional 8 wk. *Spirulina* supplementation lowered intimal surface of the aorta by 32.2 to 48.3%, compared to HCD. Serum triglyceride (TG) and total cholesterol (TC) significantly were reduced in SP groups. After 8 wk, serum low density lipoprotein cholesterol (LDL-C) remarkably decreased by 26.4% in SP1 and 41.2% in SP5, compared to HCD. On the other hand, high density lipoprotein cholesterol (HDL-C) was markedly increased in SP1 and SP5 compared with that in the HCD group from 2 to 8 wk. These results suggest that *Spirulina* intake can cause the reduction of hypercholesterolemic atherosclerosis, associated with a decrease in levels of serum TC, TG and LDL-C, and an elevation of HDL-C level. *Spirulina* may, therefore, be beneficial in preventing atherosclerosis and reducing risk factors for cardiovascular diseases.

Do Kyung Lee et al., (2009) reported that Lactic acid bacteria (LAB) are beneficial probiotic organisms that contribute to improved nutrition, microbial balance, and immunoenhancement of the intestinal tract, as well as lower cholesterol. Although present in many foods, most trials have been in spreads or dairy products. Here the researchers tested whether Bifidobacteria isolates could lower cholesterol, inhibit harmful enzyme activities, and control fecal water content. In vitro culture experiments were performed to evaluate the ability of Bifidobacterium spp. isolated from healthy Koreans (20~30 years old) to reduce cholesterol-levels in MRS broth containing polyoxyethanylcholesterol sebacate. Animal experiments were performed to investigate the effects on lowering cholesterol, inhibiting harmful enzyme activities, and controlling fecal water content. For animal studies, 0.2 ml of the selected strain cultures $(10^8 \sim 10^9 \text{ CFU/ml})$ were orally administered to SD rats (fed a highcholesterol diet) every day for 2 weeks. B. longum SPM1207 reduced serum total cholesterol and LDL levels significantly (p < 0.05), and slightly increased serum HDL. B. longum SPM1207 also increased fecal LAB levels and fecal water content, and reduced body weight and harmful intestinal enzyme activities. Daily consumption of B. longum SPM1207 can help in managing mild to moderate hypercholesterolemia, with potential to improve human health by helping to prevent colon cancer and constipation.

Changlu Ma et al., (2019) isolated about 85 strains of lactic acid bacteria from corn silage and analyzed in vitro for their cholesterol removal, NPC1L1 protein down-regulation and bile salt deconjugation ability, respectively. Nineteen strains were selected for further analysis for their probiotic potential. Finally, 3 strains showing better probiotic potential were evaluated for their cholesterol-lowering activity in hamsters. The strains showing the greater cholesterol removal and NPC1L1 protein down-regulation activity had no significant effects on serum and hepatic cholesterol levels in hamsters (p > 0.05). However, Lactobacillus *plantarum* CAAS 18008 (1×10^9 CFU/d) showing the greater bile salt deconjugation ability significantly reduced serum low-density lipoprotein cholesterol, total cholesterol, and hepatic total cholesterol levels by 28.8%, 21.7%, and 30.9%, respectively (p < 0.05). The cholesterollowering mechanism was attributed to its bile salt hydrolase activity, which enhanced daily fecal bile acid excretion levels and thereby accelerated new bile acid synthesis from cholesterol in liver. This study demonstrated that the strains showing greater cholesterol removal and NPC1L1 protein down-regulation activity in vitro hardly reveal cholesterollowering activity in vivo, whereas the strains showing greater bile salt deconjugation ability in vitro has large potential to decrease serum cholesterol levels in vivo.

3. Evaluating the cytotoxic effect and influence of FSL on human colon cancer cell line Caco-2

It has been reported very significantly about the anticancer properties of *Spirulina* spp worldwide. Agnieszka Smieszek et al., (2017) studied the anticancer properties of Spirulina platensis (SP) on human colon cancer cell line (Caco-2). It is a blue-green microalga that has recently raised attention not only as a nutritional component, but also as a source of bioactivities that have therapeutic effects and may find application in medicine, including cancer treatment. In their study the researchers determined the cytotoxic effect of S. platensis filtrates (SPF) on human colon cancer cell line Caco-2. Three concentrations of SPF were tested—1.25%, 2.5%, and 5% (v/v). Researchers have found that the highest concentration of SPF exerts the strongest anti-proliferative and pro-apoptotic effect on Caco-2 cultures. The SPF negatively affected the morphology of Caco-2 causing colony shrinking and significant inhibition of metabolic and proliferative activity of cells. The wound-healing assay showed that the SPF impaired migratory capabilities of Caco-2. This observation was consistent with lowered mRNA levels for metalloproteinases. Furthermore, SPF decreased the transcript level of pro-survival genes (cyclin D1, surviving, and c-Myc) and reduced the autocrine secretion of Wnt-10b. The cytotoxic effect of SPF involved the modulation of the Bax and Bcl-2 ratio and a decrease of mitochondrial activity, and was related with increased levels of intracellular reactive oxygen species (ROS) and nitric oxide (NO). Moreover, the SPF also caused an increased number of cells in the apoptotic sub-G0 phase and up-regulated expression of mir-145, simultaneously decreasing expression of mir-17 and 146. Obtained results indicate that SPF can be considered as an agent with anti-cancer properties that may be used for colon cancer prevention and treatment.

Very recently, Braune et al., (2021) reported that the application of cytostatic drugs or natural substances to inhibit cancer growth and progression is an important and evolving subject of cancer research. There has been a surge of interest in marine bioresources, particularly algae, as well as cyanobacteria and their bioactive ingredients. Dried biomass products of *Arthrospira* and *Chlorella* have been categorized as "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA). Of particular importance is an ingredient of *Arthrospira:* phycocyanin, a blue-red fluorescent, water-soluble and non-toxic biliprotein pigment. It is reported to be the main active ingredient of *Arthrospira* and

was shown to have therapeutic properties, including anti-oxidant, anti-inflammatory, immune-modulatory and anticancer activities. In the present review, in vitro and in vivo data on the effects of phycocyanin on various tumor cells and on cells from healthy tissues are summarized. The existing knowledge of underlying molecular mechanisms, and strategies to improve the efficiency of potential phycocyanin based anti-cancer therapies are discussed.

Arkadiusz Czerwonka et al., (2018) reported that Spirulina is a well-described and popular dietary supplement derived from Arthrospira algae. In their study, the anticancer potential of a water extract of a commercial Spirulina product (SE) against the human nonsmall-cell lung carcinoma A549 cell line was evaluated. After qualitative analysis, the researchers investigated the effect of SE on cell viability, proliferation, and morphology. Furthermore, the influence of SE on regulation of the cell cycle, induction of apoptosis in lung cancer cells, and expression of cell cycle/apoptosis-related proteins was evaluated. Additionally, the researchers examined the cytotoxic effect of SE on normal human skin fibroblasts (HSF). Our studies revealed that SE significantly reduced cancer cell viability and proliferation, which was accompanied by cell cycle inhibition in the G₁ phase, induction of apoptosis, and prominent morphological changes. Moreover, they detected no cytotoxic effect of the tested Spirulina extract on normal skin fibroblasts. Our molecular studies demonstrated that SE reduced the phosphorylation of Akt and Rb proteins, reduced the expression of cyclin D1 and CDK4, and increased the Bax to Bcl-2 ratio in the A549 cells. In conclusion, the results obtained provide evidence of the anti-cancer activity of the commercial Spirulina product against lung cancer cells and strongly support the knowledge of the chemopreventive properties of Spirulina.

Renata Koníckova et al (2014) highlighted the application of *Spirulina platensis* as a as a dietary supplement due to its hypocholesterolemic properties. Among other bioactive substances, it is also rich in tetrapyrrolic compounds closely related to bilirubin molecule, a potent antioxidant and anti-proliferative agent. The aim of our study was to evaluate possible anticancer effects of *S. platensis* and *S. platensis-derived* tetrapyrroles using an experimental model of pancreatic cancer. The anti-proliferative effects of *S. platensis* and its tetrapyrrolic components [phycocyanobilin (PCB) and chlorophyllin, a surrogate molecule for chlorophyll A] were tested on several human pancreatic cancer cell lines and xenotransplanted nude mice. The effects of experimental therapeutics on mitochondrial reactive oxygen species (ROS) production and glutathione redox status were also evaluated. Compared to untreated cells,

experimental therapeutics significantly decreased proliferation of human pancreatic cancer cell lines *in vitro* in a dose-dependent manner (from 0.16 g-L-1 [S. *platensis*], 60 μ M [PCB], and 125 μ M [chlorophyllin], p<0.05). The anti-proliferative effects of *S. platensis* were also shown *in vivo*, where inhibition of pancreatic cancer growth was evidenced since the third day of treatment (p < 0.05). All tested compounds decreased generation of mitochondrial ROS and glutathione redox status (p = 0.0006; 0.016; and 0.006 for *S. platensis*, PCB, and chlorophyllin, respectively). In conclusion, *S. platensis* and its tetrapyrrolic components substantially decreased the proliferation of experimental pancreatic cancer. These data support a chemopreventive role of this edible alga. Furthermore, it seems that dietary supplementation with this alga might enhance systemic pool of tetrapyrroles, known to be higher in subjects with Gilbert syndrome.

CONCLUSION

Functional foods have raised within the industrial production era. In this context, microalgae have become an innovative and promising resource of nutritional supplements as they are commercially cultivated to produce valuable compounds, including protein, pigments, lipids, essential amino acids, monounsaturated and polyunsaturated fatty acids, carotenoids, steroids and vitamins, among others. Specifically, Spirulina platensis which has recognized as safe (GRAS) for human consumption, provides important properties such as anti-cancer and anti-hypertensive activity, immune system enhancement, high content of antioxidants, vitamins and trace elements and belongs to the category of superfoods. Spirulina shows strong invulnerable animating impacts, shows antiviral movement against an assortment of hurtful infections. It appears guarantee as a malignant growth precaution operator and in the treatment of tumours. Spirulina appears far extending cardiovascular advantages counting improvement of blood lipid profiles, aversion of atherosclerosis, and control of hypertension. Notwithstanding high levels of provitamin A, dried smaller scale green growth can give different supplements including proteins, minerals, nutrients, and cancer prevention agents. World creation of consumable green growth and green growth items to be utilized as dietary enhancements, nourishment added substances, practical nourishments, and medications has arrived at a huge number of tons every year after research which has demonstrated its significance.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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